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OF

# INTERNAL MEDICINE

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# CONTENTS OF VOLUME 43

JANUARY, 1929 NUMBER 1

	PAGE
Aneurysm of the Coronary Arteries Maurice Packard, M D, and H F Wechsler, M D, New York	1
The Effect of Roentgen Rays on the Heart II The Microscopic Changes in the Heart Muscle of Rats and of Rabbits Following a Series of Exposures Aldred S Warthin, M D, Ph D, LL D, and Ernst A Pohle, M D, Ph D, Ann Arbor, Mich	15
The Heart in Thyroid Disease I Changes in the T Wave of the Human Electrocardiogram Following Iodine Medication and Thyroidectomy Walter W Hamburger, M D, Morris W Lev, M D, Walter S Priest, M D, and Helen C Howard, Chicago	35
Specific Serum Treatment in Chronic Ulcerative Colitis J Arnold Bargen, M D, Rochester, Minn	50
The Relation of the Hiatus Esophageus of the Diaphragm to the Stomach An Important Function of the Pillars of the Diaphragm Minas Joannides, M D, Chicago	61
Normal Rhythm of White Blood Cells in Women Christianna Smith, Ph D, and Anna Mary McDowell, M A, South Hadley, Mass	68
Fatal Phenobarbital Poisoning Report of a Case with Toxicologic Analysis Harold N Wright, M Sc, Minneapolis	85
Mustard Gas and Tuberculosis An Experimental Study Amos R Koontz, M D, Baltimore	90
Normal Blood Determinations in the South Maxwell M Wintrobe, M D, and Morell W Miller, M D, New Orleans	96
Experimental Bile Peritonitis and Its Treatment in the Dog O H Horrall, M D, Ph D, Chicago	114
Hyperbilirubinemia in Peptic Ulcer Mills Sturtevant, M D, and Robert Pulley Wallace, M D, New York	129
Clinical Spirography Spirograms and Their Significance Johannes M Nielsen, M D, and Paul Roth, M D, Battle Creek, Mich	132
Albuminuria in the Mechanism of Detoxification Edmund Andrews, M D, William A Thomas, M D, and William F Welker, M D, Chicago	139
Book Reviews	144

FEBRUARY, 1929 NUMBER 2

Can the Gallbladder Empty Through Duodenal Biliary Drainage? Is the Gallbladder the Source of "B" Bile? A Cholecystographic Study of Biliary Drainage B B Vincent Lyon, M D, Philadelphia	147
Gallop Rhythm in Hypertension Herman Mond, M D, and Enid Tribe Oppenheimer, B Sc, New York	166
Experimental Heart Block Clayton J Lundy, M D, and Lewis W Woodruff, M D, Chicago	184
The Excursion of the Costal Margins in Health and in Disease H A Bray, M D, and J L Wilson, M D, Ray Brook, N Y	187
Ochronosis Report of a Case of Carbolochronosis S E Goldberg, M D, Detroit	196

FEBRUARY—Continued

	PAGE
Opium Addiction I The Conduct of the Addict in Relation to Investigative Study Arthur B Light, M D, and Edward G Torrance, M D, Philadelphia	206
The Radicular Syndrome in Hypertrophic Osteo-Arthritis of the Spine An Analysis of Thirty Cases Lewis Gunther, M D, and William J Kerr, M D, San Francisco	212
The Cardiovascular Problem in Pneumonia B M Randolph, M D, Washington, D C	249
Impaired Auriculoventricular Conduction in Rheumatic Fever A Comparative Study with Diagnostic Applications Robert L Levy, M D, and Kenneth B Turner, M D, New York	267
Cultural and Serologic Reactions with Green-Producing Micrococci from Measles N S Ferry, M D, and Arlyle Noble, A B, Detroit	274
Book Reviews	295

MARCH, 1929 NUMBER 3

Peptic Ulcer The Effect of Parenteral Injections of Purified Milk Proteins on the Symptoms and Progress Lay Martin, M D, Baltimore	299
Opium Addiction II Physical Characteristics and Physical Fitness of Addicts During Administration of Morphine Arthur B Light, M D, and Edward G Torrance, M D, Philadelphia	326
The Ventricular Electrocardiogram An Experimental Study Harold L Otto, M D, New York	335
Chronic Pulmonary Infection Due to the Friedlander Bacillus A Clinical and Roentgenologic Study Leon H Collins, Jr, M D, and Karl Kornblum, M D, Philadelphia	351
The Cholesterol Content of Blood Plasma in Diabetes Mellitus A Statistical Study Based on Two Thousand Observations in Three Hundred and Eighty-Five Cases I M Rabinowitch M D, Montreal	363
The Cholesterol Content of Blood Plasma in Juvenile Diabetes A Statistical Study I M Rabinowitch, M D, Montreal	372
Diabetes Mellitus A Study of One Hundred and Forty-Seven Autopsies William F Gibb, Jr, M D, and Victor W Logan, M D, New York	376
The Effect of Synthalin on the Respiratory Quotient of the Diabetic Patient W G Karr, Ph D, C Schumann, M D, and O H Petty, M D, Philadelphia	384
The Reducing Power (Blood Sugar) of Filtrates from the Blood of the Rabbit Ernest L Scott, Ph D, with the Technical Assistance of Louis B Dotti, New York	393
Pancreatic Function III The Pancreatic Secretion in Disturbed Gastric Secretion Seizaburo Okada, M D Tsunamoto Imazu, M D, Kwanichi Kuramochi, M D Masaka Matsubara, M D, and Toshio Tsukahara, M D, Tokyo, Japan	413
Correlation of the Aorta A Case of the Adult Type in a Child Six Months of Age A M Sola, M D, and I Nachamie, M D, New York	420
Book Reviews	425

APRIL, 1929 NUMBER 4

Colds and Asthma Associated with Colds Preventive Treatment with Vaccines I Chandler Walker, M D, Boston	429
----------------------------------------------------------------------------------------------------------	-----

# CONTENTS OF VOLUME 43

## APRIL—Continued

	PAGE
Pancreatic Function IV The Humoroneural Regulation of the Gastric, Pancreatic and Biliary Secretions Seizaburo Okada, M D , Kwanichi Kuramochi, M D , Toshio Tsukahara, M D , and Tatsuo Ooinoue, M D , Tokyo, Japan	446
The Andrewes Diazo Reaction in Nephritis J S Eastland, M D , and E G Schmidt, Ph D , Baltimore	472
Perforations of the Colon in Chronic Ulcerative Colitis J Arnold Bargen, M D , and Minard F Jacobs, M D , Rochester, Minn	483
The Metabolism in Pernicious Anemia Howard L Alt, M D , Boston	488
Alkalosis Occurring in Anemia (Probably Pernicious) Report and Comment on a Case Lewis F Frissell, M D and John Staige Davis, Jr , M D , New York	504
Bronchogenic Squamous Cell Carcinoma Report of a Case Associated with Pleural Effusion and Pulmonary Osteo-Arthropathy, with Features That Simulated Infection by Endameba Histolytica Ralph G Mills, M D , Rochester, Minn , and Nolie Mumey, M D , Denver	516
The Identity of So-Called Agranulocytic Angina Report of a Case Edward Rose, M D , and Karl Musser Houser, M D , Philadelphia	533
The Discordant Electrocardiogram Harold L Otto, M D , New York	549
Opium Addiction III The Circulation and Respiration of Human Addicts During the Administration of Morphine Arthur B Light, M D , and Edward G Torrance, M D , Philadelphia	556
Book Reviews	568

## MAY, 1929 NUMBER 5

The Bacteriology of the Blood and Joints in Chronic Infectious Arthritis Russell L Cecil, M D , Edith E Nicholls, M D , and Wendell J Stansby, M D , New York	571
Clinical Significance of Premature Beats, with Particular Reference to Heart Rate James W Esler, M D , Washington, D C , and Paul D White, M D , Boston	606
Chloride Metabolism and Alkalosis in Alkali Treatment of Peptic Ulcer Herbert A Wildman, M D , Wooster, Ohio	615
Cutaneous and Venous Blood Sugar Curves II In Benign Glycosuria and in Diabetes Myer Friedenson, M K Rosenbaum, E J Thalheimer, and J P Peters, M D , New Haven, Conn	633
Auricular Fibrillation Results of Seven Years' Experience with Quinidine Sulphate Therapy (1921 to 1928) Louis Wolff, M D , and Paul D White, M D , Boston	653
The Effect of Digitalis on the Electrocardiogram An Experimental Study on Dogs and Cats William A Brams, M D , Chicago	676
Opium Addiction IV The Blood of the Human Addict During the Administration of Morphine Walter G Karr, Ph D , Arthur B Light, M D , and Edward G Torrance, M D , Philadelphia	684
The Rôle of Allergy in Tuberculosis Arnold Rice Rich, M D , Baltimore	691
Studies in Fat Metabolism II The Character of Blood Lipids in Hepatic Disorders, Including Migraine C W McClure, M D , and Mildred E Huntsinger, B S , Boston	715
Book Reviews	731

The Adrenal Glands	G N Stewart, M D, Cleveland	733
The Pathogenesis of Aspiratory Abscess of the Lung Its Possible Relation to Abscess of the Lung Following Tonsillectomy	Joseph Harkavy, M D, New York	767
Insulin in Acromegalic Diabetes	Helmuth Ulrich, M D, Boston	785
Clinical Types of Edema in the Heart Failure of Childhood	Harrold A Bachmann, M D, Chicago	795
Pathologic Changes in Auricular Fibrillation and in Allied Arrhythmias	Wallace M Yater, M D, Washington, D C	808
The Variability of Blood Pressure Morning and Evening Studies	H S Diehl, M D, Minneapolis	835
Peptic Ulcer A Study of Five Hundred and Fifty-Six Cases	Edward S Emery, Jr, M D, and Robert T Monroe, M D, Boston	846
Some Medicolegal Aspects of Occupational Disease	Henry H Kessler, M D, Newark, N J	874
Opium Addiction V Micellaneous Observations on Human Addicts During the Administration of Morphine	Arthur B Light, M D, and Edward G Torrance, M D, Philadelphia	878
Book Reviews		890
General Index		893

## ANEURYSM OF THE CORONARY ARTERIES\*

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AND

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Although the coronary arteries are so frequently involved in the general diseases of the vascular system, aneurysm is an extreme rarity. In the 116 years that have elapsed since Bougon<sup>1</sup> (1812) reported the first case, after a careful search of the literature we have been able to collect only thirty-one examples of this condition—and at least two of these are extremely doubtful. This total does not include cases of periarteritis nodosa, a disease entity first described by Kussmaul and Maier<sup>2</sup> in 1866. The multiple beadlike aneurysms of the coronary arteries, which are frequently present in this disease, are only part of a widespread involvement of the medium sized vessels throughout the body and are best considered from that standpoint.

Few attempts have been made to collect the scattered case reports and to analyze them critically. The most elaborate of these are Crisp<sup>3</sup> (1871), eleven cases, Capps<sup>4</sup> (1899), nineteen cases, and Griffith<sup>5</sup> (1901), twenty-four cases. Their tables, however, are incomplete and contain data for many cases in which there were no aneurysm of the coronary artery. For the sake of future workers in this field, it might be well to point out these errors. In the cases of Ward<sup>6</sup> and Stevenson<sup>7</sup> and in the specimen at St. Bartholomew's Museum<sup>8</sup> the aneurysms were of the sinus of Valsalva. That of Bristowe<sup>8</sup> and the one listed in the St. Thomas' Museum Catalogue and reported by Powell<sup>9</sup> are cases of periarteritis nodosa. In the case of Clark<sup>10</sup> the rupture of a coronary artery was not the seat of an aneurysm, and Shrady's<sup>11</sup> report

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\* From the Medical Service of the Gouverneur Hospital.

1 Bougon. *Biblioth. méd.* **37**, 183, 1812.

2 Kussmaul and Maier. *Deutsche Arch. f. klin. Med.* **1**, 484, 1865-1866.

3 Crisp. *Tr. Path. Soc. London* **22**, 106, 1871.

4 Capps. *J. A. M. Sc.* **118**, 312, 1899.

5 Griffith. *Brit. M. J.*, 1901, p. 266.

6 Ward. *Tr. Path. Soc. London* **8**, 134, 1857.

7 Stevenson, quoted by Crisp (footnote 3), p. 33.

8 Bristowe. *Tr. Path. Soc. London* **7**, 98, 1856.

9 Powell, Reynolds. *System of Medicine*, New York, The Macmillan Company, 1879, vol. 5, p. 133.

10 Clark. *New York M. J.* **8**, 384, 1860.

11 Shrady. *New York M. Press* **3**, 225, 1860.

is merely an abstract of Clark's case Wiegand<sup>12</sup> reported one case of aneurysmal dilatation of the ascending aorta, associated with coronary sclerosis Griffith<sup>5</sup> referred to the report of a second case in the *St Bartholomew Hospital Reports* for 1871, but we have been unable to discover any mention of it in that journal He also listed two cases by Dr Chadwick of Leeds, who "remembers having heard of them—one in the practice of one of his colleagues and the other in or about the hospital" For obvious reasons, these have not been included in our tables

Eppinger,<sup>13</sup> who is not listed by either Capps or Griffith, described two cases, one of which is definitely periarteritis nodosa He also mentioned a case recorded by Thompson<sup>14</sup> The latter exhibited multiple aneurysms on the basis of an acute endocarditis, none of which, however, involved the coronary arteries Baly's<sup>15</sup> case of thrombosis of the coronary artery was also excluded by Griffith

Because of the meager descriptions of the heart and especially of the other organs of the body, and of the lack of adequate microscopic study in many of the cases reported, it has been impossible to decide on the exclusion of a few cases retained in our tables The condition in two cases, particularly (Clarke<sup>16</sup> and Heuse<sup>17</sup>), is in all probability periarteritis nodosa In addition, several other cases, such as those reported by Gee<sup>18</sup> and Malet and Evans,<sup>19</sup> are puzzling and unique The data for two cases (Malmsten<sup>20</sup> and Herczel<sup>21</sup>) were unavailable

#### ETIOLOGIC FACTORS

*Sex*—Coronary aneurysm is almost three times as common in males as in females In the twenty-five cases in which the sex was mentioned, eighteen were males and seven females

*Age*—Information concerning age is given in twenty-three cases in this series The youngest patient was 5 and the oldest 77 years of age One patient (Bougon) is described as being old As can be seen from table 1, there is not a marked predilection for any decade

*Trauma*—In only three cases is indirect trauma considered as a possible etiologic factor Peacock's<sup>22</sup> patient was a lifter of great

12 Wiegand *Med Convers Blatt* **1** 217, 1830

13 Eppinger *Arch f klin Chir* **35** 1, 1887

14 Thompson *M Times & Gaz* **2** 56, 1877

15 Baly *Pathol Tr* **3** 264, 1850-1852

16 Clarke *Pathol Tr* **47** 24, 1896

17 Heuse *Bull Acad roy de med de Belg* **15** 492, 1856

18 Gee *St Bartholomew Hosp Rep* **7** 148, 1871

19 Malet and Evans *Lancet* **2** 67, 1887

20 Malmsten *Aorten-Aneurysmens Etiologie*, Stockholm, 1888

21 Herczel *Orvosı hetı szemle* **36** 149, 1904

22. Peacock *Tr Path Soc. London* **1** 227, 1846-1848, **9** 592, 1849

weights, the patient in Crisp's<sup>3</sup> case suffered a prolonged submersion in water and a fall from a scaffold, while Fraenkel's<sup>23</sup> patient sustained wounds in the arm and head and severe shock

*Chronic Cardiovascular Disease*—Seven patients gave a history of rheumatic fever and one of rheumatic pains. Only three patients, including our own, exhibited a syphilitic meso-aortitis. One patient had had scarlatinal nephritis, one generalized arteriosclerosis and one cardiac disease

#### SYMPTOMATOLOGY, PHYSICAL SIGNS AND DIAGNOSIS

There are not any typical symptoms referable to the aneurysm itself. In fact, in many cases there were apparently no complaints, or they were unknown at the time of the sudden death of the patient, either in the street or after such exertion as coitus.

Exclusive of a few unusual cases, the symptoms, when present, fall into two distinct groups. (1) There is a history of rheumatic fever

TABLE 1—*Incidence of Aneurysm of the Coronaries According to the Age of the Patient*

Age	Number
0 to 10	2
10 to 20	3
20 to 30	4
30 to 40	5
40 to 50	2
50 to 60	1
60 to 70	4
70 to 80	2

with or without longstanding chronic valvular disease, and also the symptoms of an acute or subacute bacterial endocarditis, (2) the symptoms are those either of angina pectoris or of myocardial degeneration on a coronary basis.

In Ruge's<sup>24</sup> case, there was an acute osteomyelitis of the femur with pyemia, while in the case reported by Malet and Evans,<sup>19</sup> the only symptoms were thirst and polyuria. The patient in Capps'<sup>4</sup> second case had a hemiparesis, numbness and tingling in the feet and convulsions, probably due to a coincident syphilis of the central nervous system. Gee's<sup>18</sup> case, a child, aged 7, had a scarlatinal dropsy and died of an intercurrent pneumonia with meningitis.

Sudden death is common and is practically always due to rupture of the aneurysm. Gradual heart failure is the cause of death in the others.

*Physical Observations*—There is nothing characteristic about the physical signs to differentiate the condition. They depend entirely on

23 Fraenkel. *Deutsche med Wchnschr* 43 159, 1917

24 Ruge. *Deutsche Ztschr f Chir* 80 150, 1905



the underlying pathologic changes—acute and subacute bacterial endocarditis and coronary disease—and the degree of cardiac decompensation

A pathognomonic sign has not been described in the few cases actually observed at the time of rupture

*Diagnosis*—From the foregoing, it is obvious that an antemortem diagnosis of coronary aneurysm is impossible, and it was not mentioned as a possibility in any of the cases in our series

#### PATHOLOGIC OBSERVATIONS

The site of the aneurysm is stated in twenty-seven cases. The left coronary artery is the one most commonly affected, and in the vast majority, it is single. Multiple aneurysms were present in only six cases. The actual sites were as follows: left coronary, seventeen, right coronary, six, both coronaries, four. The bilateral cases include the doubtful ones of Heuse<sup>17</sup> and Clarke<sup>16</sup> and the unclassifiable one of Gee<sup>18</sup>. When the aneurysm is single, it is practically always situated immediately beyond the coronary orifice within the first inch of its course. The others, including the multiple aneurysms, are usually found at the points of division of the artery.

The aneurysms vary in size from that of a pea to that of a pigeon's egg. The largest was described by Martland<sup>25</sup> as being 6 cm. in diameter.

Rupture occurred in fourteen, or in nearly 50 per cent of the cases in our series. As described by Vestberg,<sup>26</sup> the aneurysm bursts first into the undefended or periaortic space, and then into the pericardial sac. In two cases (Sommer,<sup>27</sup> Windholz<sup>28</sup>), the perforation was into the conus arteriosus of the pulmonary artery.

Disregarding the few unique cases, the aneurysms themselves can be divided into two classes: (1) mycotic-embolic and (2) arteriosclerotic.

*Mycotic-Embolic Aneurysm*—This term implies the synergistic action of two factors—the embolus itself and the mycosis or infection—and must be differentiated, on the one hand, from the pure mycotic aneurysm, of which we have an example in our series (Ruge), and on the other, from the pure embolic aneurysm, such as a calcareous plaque.<sup>29</sup>

Although as early as 1851, Koch<sup>30</sup> and, after him, several others,<sup>31</sup> described the association of an aneurysm of a terminal artery with an

25 Martland Proc New York Path Soc **17** 34, 1917

26 Vestberg Nord med Ark **7** 1, 1897

27 Sommer Frankfurt Ztschr f Path **5** 98, 1910

28 Windholz Centralbl f allg Pathol u path Anat **37** 385, 1926

29 Libman Proc New York Path Soc **5** 88, 1905

30 Koch, L Inaug Diss Erlangen, 1851

31 Tufnell Dublin Quart J M Sc **15** 371, 1853 Waterman West M J **2** 584, 1867

acute endocarditis of the aortic valve, Ponfick<sup>32</sup> is usually credited with being the first to recognize the connection between the endocardial vegetations and the peripheral aneurysms. He believed that they were caused by embolic calcified vegetations. In 1864, however, Ogle<sup>33</sup> definitely attributed the aneurysms present in his case to emboli from an aortic endocarditis. The inflammatory nature of the lesion was first established by Eppinger<sup>34</sup> in his exhaustive survey of the subject. Since that time, although many similar cases have been reported, they are not common, being only comparatively frequent in the subacute and chronic ulcerative forms of endocarditis. The incidence of aneurysm in the latter conditions can be gathered from the statistics of Lubarsch<sup>35</sup>. In 137 cases of subacute bacterial endocarditis and the recurrent chronic necrotizing form, he found embolic aneurysms in 10.2 per cent. The coronary arteries escaped entirely. In a large collection of cases the superior mesenteric artery was the vessel most commonly affected.

In our series, there are seven cases (Bougon,<sup>1</sup> Ogle,<sup>33</sup> Eppinger,<sup>34</sup> Griffith<sup>5</sup> [cases 1 and 2], Henke,<sup>35</sup> Lublin<sup>36</sup>) which definitely belong in this category. Toller's<sup>37</sup> case probably belongs to this group, but unfortunately the condition of the heart valves is not mentioned. In three cases (Peacock,<sup>22</sup> Capps<sup>4</sup> [case 2], Windholz<sup>28</sup>), a healed chronic endocarditis was found, and the question naturally presents itself as to the possible etiologic significance of the acute stage of the process. After careful examination, we are inclined to place these cases in the arteriosclerotic group.

Of the seven unquestionable cases, only one was multiple and bilateral. The average age of the patients was 27. Rupture occurred in two cases (Ogle, Henke).

Depending on the stage of the process, the wall of the aneurysm is composed of varying amounts of relatively recent fibrous tissue, remnants of elastic fibers and more or less smooth muscle belonging to the media. At the entrance to the aneurysm, the intima and elastica cease abruptly and, at times, the ends of the latter have a curled appearance. Occasionally, a hyaline thrombus is found adherent to the floor. According to the completeness of the rupture, hemorrhage is present either in the adventitia or in the surrounding tissues. The wall is infiltrated with polymorphonuclear leukocytes and round cells. Plasma cells and endothelioid cells that contain blood pigment are often present. Streptococci or staphylococci are the usual causative bacteria.

32 Ponfick *Virchows Arch f path Anat* **58** 528, 1873

33 Ogle *St George's Hosp Rep* **2** 285, 1867

34 Henke and Lubarsch *Handb d spez path anat u histol* **2** 710, 1924

35 Henke *Centralbl f allg Pathol u path Anat* **21** 1003 1910

36 Lublin *Centralbl f Herzkrankh u Gefasskrankh* **12** 171, 1920

37 Toller *St Thomas' Hosp Rep, Lond* **31** 357, 1904

TABLE 2.—*Report of Cases of Aneurysm in the Literature*

Author	Age	Sex	Occupation	Previous History	Symptoms and Physical Conditions	Site	Size	Rupture	Coronaries	Additional Pathologic Changes
1 Bouillon, 1812	Old	M	Soldier	Attacks of low fever and then mania	For four years, nocturnal anginal attacks, six weeks ago, fever and pain in calf of leg, sudden death	Right		+	Right dilated to size of female sound	Venulations on aortic valves contracting orifice to the size of a little finger
2 Murat (Dict. des sc. med. 5, 1811, 1813)	10	M			No cardiac symptoms	Left	Small nut	0		
3 Herdum (A. Otto's Compensum of Human and Comparative Anatomy, London, 1831, p. 119)	77	M	Carrier	Good health	Twenty-eight months ago, apoplexy with left hemiplegia four days before death, malaise, vomiting, dyspnea and precordial pain, sudden death	Left	Large nut	+	Left dilated to the size of a brachial artery, calcified	Transverse rupture of the left ventricle, enlargement of the aorta
5 Peacock, 1846	51	M	Butcher	Irregular habits, lighter of weights, rheumatic pains	For months, severe cough and dyspnea, admitted in collapse ten days before death, with rapid feeble pulse, rapid respirations and cough, death by gradual cardiac failure	Left	Pigeon's egg	0	Dilatation and marked ossification of the left, right slightly dilated with scattered calcified plaques	Edematous, pericarditis, slight thickening and adherence of aortic cusps, several calcified plaques in the aorta
6 Hulse, 1856	21	M	Funeral	Three attacks of intermittent fever	For three months, symptoms of cardiac decompensation, hydrothorax, ascites, anasarca, sudden death	Both	5 to 9 mm in diameter	+	Rupture of coronaries in two places	Valves normal
7 Thinnell (New York M. J. 16, 82, 1876)	25	F			Sudden death	Right		0		
8 Markoe (New York M. J. 4, 88, 1860)		F			Sudden death		End of little finger	+	Atheroma of artery	Atheroma of aorta
9 Wood, 1860		M			Sudden death during coitus					

10	Ogle, 1867	26	M	Blacksmith	Rheumatic fever twelve years ago	Two and one half years ago, pain in back of the head followed in two weeks by numbness in the thumb and first two fingers of the right hand and pains in the back, arms and abdomen similar attack a month ago with paralysis of the arm and dropped wrist murmur at the apex, sudden death	Three 1 Left 2 Right 3 Right	Pet Slightly larger than pet Cobnut +	0 0 +	Acute endocarditis of the aortic valve, aneurysmal pouches of the brachial artery, renal infarcts (?)
11	Buchner 1867	17	M	Palater		For ten months, irregular attacks at times associated with palpitation more frequent in past six weeks, blowing murmur over the entire precordium sudden death	Left	6 cm in diameter	0	Dilatation of the proximal portion of left, bony plaques on the floor of the aneurysm
12	Gee, 1871	7	M			Died of scutimal dropsy with intercurrent pneumonia and meningitis	Three 1 Left 2 Right 3 Right	Pet Pet Horse-bean Walnut	0 0 0 +	Dilatation of the right and posterior sinuses of Aorta, fibrinopurulent pericarditis
13	Clibbe, 1871	63	M	Carpenter	Prolonged submersion twenty years ago, fall from scaffold three years ago, intemperate	Large hematemesis three and one half months ago sudden death	Right	Walnut	+	Valves healthy aortic cusps of mitral presented spurs of atheroma
14	Mallet and Evans, 1887	5	M			For three weeks intense thirst and polyuria pale and emaciated two small unhealthy sores on the face and one on the leg sudden death	Left	Pet	+	Valves normal slight atheroma of the aorta
15	Uppinder, 1887	25	F		Pain in the ankle joints and fever four years ago since then symptoms of cardiac disease	For two months, sticking pains in the chest and abdomen cough fever ischtes and in aortic systolic murmur at apex and over right side of the heart	Left	5 mm long	0	Chronic endocarditis of the aortic and mitral valves with fresh vegetations on the latter aneurysm of the splenic artery acute hemorrhagic nephritis

TABLE 2—*Report of Cases of Aneurysm in the Literature—Continued*

Author	Age	Sex	Occupation	Previous History	Symptoms and Physical Conditions	Site	Size	Rupture	Coronaries	Additional Pathologic Changes
16 Clark, 1898	10	F			One month ago sucking half the size of a walnut on right buttock three weeks later, similar lump in the left axilla, sudden death	Dozen on both	Pea to small chestnut	+	Inner coats of the coronaries and branches greatly thickened	Fibrous ring of thickening on the mitral, but no recent vegetations, aneurysm in left axilla not proved
17 Capps, 1889	About 10	M			Found dead in street	Left	Pigeon's egg	0	Anterior branch of left thickened, posterior branch calcified, slight atheromatosis of the right	Valves normal, slight atheromatosis of the aorta
18 Capps, 1899	39	M	Telegraph operator	Syphilis several years ago, one year ago, left hemiparesis, alcohol to excess	For four weeks, numbness and tingling in the legs and feet and later over the whole body, convulsions, died of broncho pneumonia	Two Left	1 Hazel nut 2 Smaller	0	Wall of the left coronary streaked with yellowish spots and calcareous scales	Syphilitic aortitis with early aneurysm, bulging of interventricular septum, aortic valves tough, thickened and sclerosed
19 Griffith, 1901	19	F			Rheumatic pains in both knees one year ago, symptoms of nephritis nine months afterward, diagnosis of mitral disease, at that time symptoms of acute endocarditis	Right	Pea	0	Wall of the aneurysm tough and fibrous	Subacute bacterial endocarditis of the mitral and aortic valves
20 Griffith, 1901	45	F		Rheumatism at 14	Old mitral disease with heart failure	Right	Orange pip	0	Atheromatous patches in both and slight tortuosity	Subacute bacterial endocarditis of aortic and mitral valves, old infarcts of spleen and kidneys
21 Toller, 1901	40	M	Soldier	Rheumatic fever	Shortness of breath on exertion, cardiac pain with cough and occasional vomiting, a few weeks later slight ascites and transient edema of the eyelids systolic murmur over the lower end of the sternum, developed generalized anasarca, paralysis of left vocal cord and consolidation of the right apex of the lung, gradual cardiac failure	Left	Hens egg	0	Left negative below aneurysm, right sclerotic	Valves (?), concretio cordis

22 Ruge, 1905	12	M		Following abrasion of the left foot, lymphadenitis of the groin and osteomyelitis of the head of the left femur, in six weeks signs of cardiac disease and then of pyemia, hip joint resected	Left	Walnut	0	Intima of the aneurysm replaced by connective tissue, elastic fibers still visible, streptococci	Acute seropurulent pericarditis, valves normal, foramen ovale closed and veins of the lung normal
23 Winkler, 1908	68	M		Had suffered from generalized arteriosclerosis and contracted kidneys	Left		0	Both thickened and tortuous, much calcification	Scarring and brown atrophy of the heart muscle, marked arteriosclerosis of the aorta
24 Henke, 1910					Left	Cherry	0	Septic embolus in the coronary, streptococci	Ulcerative endocarditis of the aortic valve aneurysm of the mesenteric artery
25 Sommer, 1910	73	M	Laborer		Left	Two peas	+	Slight atheromatosis	Valves normal, slight general arteriosclerosis, more marked in the cerebral arteries hemorrhage into the right cerebral hemisphere
26 Marthand, 1917	32	F		Vague epigastric and precordial pain, found dead	Right	6 cm in diameter	+		Syphilitic meso pericarditis with aneurysmal dilatation
27 Fraenkel, 1917	20	M	Soldier	Wounded in the right arm and the head a year ago	Left	Half size of cherry stone	0	Aneurysm completely filled with red thrombus	Aneurysmal projection of the left ventricular wall
28 Lublin, 1920	22	M	Soldier	Rheumatic fever at 9	Left	Small	0		Recurrent verrucous endocarditis of the aortic and mitral valves left ventricular scar splenic infarct
29 Windholz, 1926	62	F		Suffered for ten years with cardiac disease and died with symptoms of decompensation	Two left	1 Nut 2 Pla	0	The first aneurysm, smaller than walls with hyaline deposits, the second rigid walls with calcified plaques	Chronic endocarditis of the aortic valve

Eppinger<sup>37</sup> believed that the mycotic embolus produced an acute inflammation of the intima at the point in which it came to rest and then spread to the adventitia by way of the vasa vasorum. From both these areas, the media next became involved, finally with a rupture of the internal elastic lamina. On the other hand, Benda<sup>38</sup> claimed that the process was an ulcerative endarteritis that invaded the media before reaching the adventitia. In all probability, both methods of progression can occur. Experimentally, the choice of route is apparently dependent on the violence of the inflammation,<sup>39</sup> the subacute following the description of Eppinger's and the acute following those of Benda.

*Arteriosclerotic Aneurysms*—We have classified the remaining cases under this heading for want of a better term and, in that, the only thing they have in common is an arteriosclerosis of the coronary arteries. In view of the extremely high incidence of coronary sclerosis and the rarity of aneurysm, this can hardly be conceived as being the only factor involved in their production. Again, it is the general consensus of opinion among pathologists that the etiologic importance of arteriosclerosis in the formation of aneurysms has been much overrated. A similar situation exists with regard to aneurysms of the cerebral arteries.

It seems to us, however, that the length of time in which a severe sclerosis has existed must not be overlooked in a consideration of this problem. That coronary sclerosis can commence at an early age—even in childhood—is generally conceded.<sup>40</sup> Monckeberg<sup>41</sup> found arteriosclerotic foci in 40 per cent of soldiers between the ages of 18 and 20. It is also well known that sufferers from severe coronary sclerosis die within a relatively short time from myomalacia, angina pectoris or coronary thrombosis. Many investigators, however, such as Gross, Oberhelman and Le Count and Spalteholz, have shown that the coronary vessels are not end arteries and that anastomoses may exist between the various branches. Dependent on the richness of the preexistent anastomoses and the slowness of progression of the sclerosis, an advanced degree of the latter can be reached and still be compatible with well being. In fact as occurred in one of our patients, a rupture of the heart itself took place without a previous history of morbidity. Given a severe sclerosis with marked degeneration and atrophy of the media plus a long period of increased intravascular tension it is interesting to speculate whether an aneurysm can develop slowly. The left

38 Benda. *Ergebn d allg Pathol u path Anat* 8 196, 1902.

39 Klotz. *Brit M J* 1 1767 1906. McMeans. *J M Research* 32 388, 1915.  
 Riches de W G, and MacLachlan, W W G. *Mycotic Embolic Aneurysms of Peripheral Arteries*, *Arch Int Med* 29 131 (Jan) 1922.

40 Wiener. *Wien klin Wchnschr* 19 725, 1906. Wiesel. *ibid* 19 723 1906.

41 Monckeberg. *Centralbl f Herzkrankh u Gefasskrankh* 8 2, 1916.

coronary preponderance and the situation of the aneurysm immediately beyond the orifice are in agreement with this point of view

Including our own, we have placed twelve cases in this group (Peste,<sup>42</sup> Peacock,<sup>22</sup> Wood,<sup>43</sup> Buchner,<sup>44</sup> Crisp,<sup>45</sup> Capps<sup>4</sup> [cases 1 and 2], Winkler,<sup>45</sup> Sommer,<sup>27</sup> Martland,<sup>27</sup> Windholz<sup>28</sup> and Packard) Of these the condition involved the left coronary artery in nine, the right coronary artery in two, and in one, the site was not stated In one case (Windholz), the left coronary artery was the seat of two aneurysms Rupture had taken place in seven cases—five into the pericardial sac and two into the pulmonary artery The average age was 57

In the vast majority of cases, the coronary artery or arteries were described as being moderately or markedly tortuous and calcified When the data are furnished, the wall of the aneurysm either is extremely thin and exhibits irregular hyaline deposits or is made rigid by scattered calcareous plaques

In the few cases in which a histologic examination of the aneurysm was made, the usual picture of an advanced arteriosclerosis was found

*Pure Mycotic Aneurysms*—The pathologic processes in this type are practically identical with those of the mycotic-embolic aneurysms that have been described Ruge reported a case of coronary aneurysm in a boy with a pyemia resulting from an osteomyelitis of the femur The heart chambers, the valves and the pulmonary veins were normal, and there was no communication between the right and the left sections of the heart

*Traumatic Aneurysms*—Direct trauma is a rare cause of aneurysm in other arteries in the body As is to be expected from their anatomic position, there is no example of it in our series Whether indirect trauma can produce a tear in the intima of the coronary and a subsequent aneurysm is a moot question Fraenkel considered his case as being of this nature The aneurysm and the lumen of the coronary were filled with a red thrombus, and an aneurysmal bulging of the left ventricle was also present

#### REPORT OF CASE

*History*—I S., a Jew, aged 60, a tailor, was admitted to the Gouverneur Hospital on Nov 18, 1927 For the past two years, he had suffered with indigestion—occasional attacks of pain and distress in the epigastrium associated with nausea On the morning of admission, he had had a typical anginal attack which however, had passed off by the time the ambulance arrived Examination revealed

42 Peste Arch gen de méd 2 472, 1843

43 Wood New York M J 8 384, 1860

44 Buchner Aneurysma der Arteria coronaria cordis sinistra, Amsterdam C G Vander Post, 1867

45 Winkler Verhandl d deutsch path Gesellsch 12 195, 1908



nothing but the presence of an inguinal hernia. He was brought to the hospital, and a few minutes later, the house physician found him dead in the admitting room.

*Autopsy*—At autopsy, the pericardial sac was distended and contained about 350 cc of fluid and clotted blood. The heart was enlarged, weighed 390 Gm and measured 15 by 12 by 8 cm. The epicardial fat was somewhat increased in amount. Both ventricles were dilated, the right more so than the left. The left ventricular wall measured from 1.4 to 1.8 cm in thickness and the right from 0.4 to 0.6 cm. The muscle was yellowish brown in color.

The mitral ring measured 12, the aortic 8.4, the tricuspid 14 and the pulmonary 8 cm in circumference. Except for the dilatation of the mitral, tricuspid and pulmonary rings the valves were grossly normal.

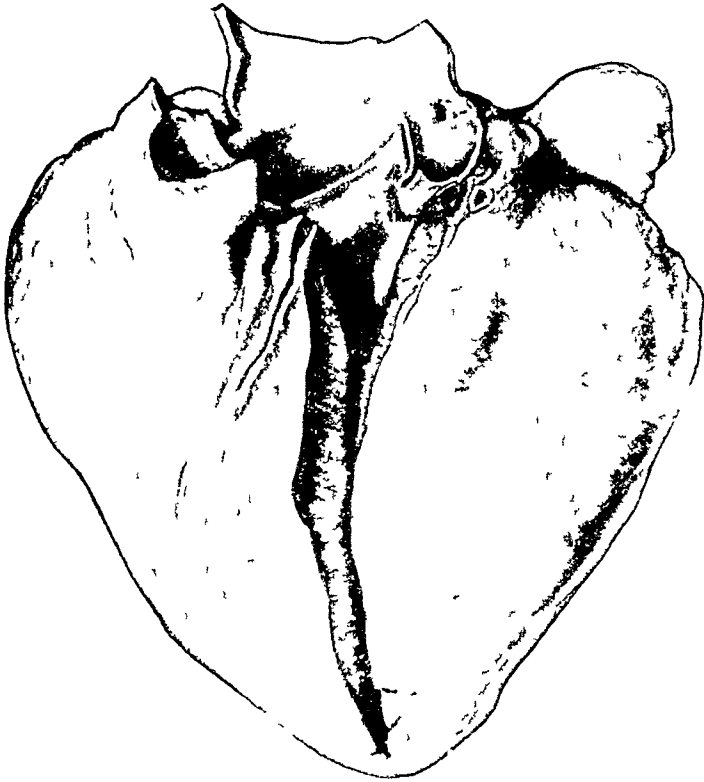


Fig 1—Aneurysm of left coronary artery

The intima of the ascending aorta, near its origin, and especially about the commissures of the aortic valves, was cloudy and showed numerous white, hyaline, grayish and grayish blue, slightly raised areas. Many of these exhibited small depressions and wrinkles. The rest of the aorta showed many yellowish streaks and patches and a few calcified plaques.

In the periaortic space, between the auricles and surrounding the root of the aorta, there was a collection of dark, clotted blood.

The coronary orifices were normal in size. Both coronaries, especially the left, were markedly sclerotic and tortuous. Situated on the left coronary artery, 1.3 cm from the orifice, there was a small globular protuberance about the size of a pea (fig 1). It lay in the auriculoventricular groove between the aorta and the left auricular appendix. On its surface, there was a small teatlike process covered by a blood clot.

When an opening was made into the vessels, the lumens were found to be patent. The atheroma and calcification commenced immediately beyond the orifices and extended down into their main branches. The protuberance on the left coronary was found to be a small aneurysmal pouch, the floor of which exhibited changes similar to those found in the rest of the artery. A probe, which was inserted into the sac, passed into the teatlike process and through a tiny perforation out into the periaortic space.



Fig 2—Syphilitic mesoaortitis,  $\times 250$

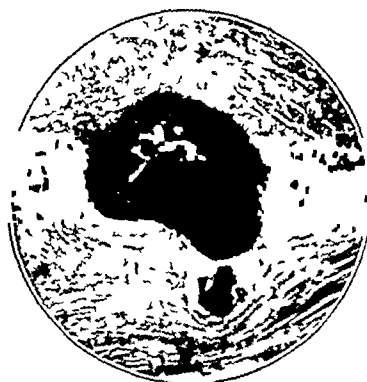


Fig 3—Coronary sclerosis,  $\times 250$

Besides hyaline and fatty degeneration of the intima, the aorta exhibited a marked round cell infiltration of the adventitia, most marked about the vasa vasorum. With the latter, it had invaded the media and produced irregularly strewn strands of scar tissue rich in wandering cells (fig 2).

The coronary vessels showed a marked atherosclerosis, with a pronounced thickening of the intima by dense, homogeneous, hyaline, connective tissue, which overlapped the area of fatty degeneration. Extensive calcification of these degenerated and necrotic foci had taken place. The internal elastic lamella was thin and frayed out at the edges of the plaques. The media was thin and atrophic (fig 3).

The heart muscle showed moderate degenerative changes and a slight interstitial fibrosis. The lungs were normal except for emphysema. The gastro-intestinal tract showed nothing of interest. The liver was somewhat enlarged, weighed 1,800 Gm and was fatty. The spleen was adherent to the surrounding structures, the capsule was thickened, weighed 150 Gm and was firmer than normal. Microscopically, the fibrous septums were thickened, and the reticular tissue was increased in amount.

The kidneys were slightly reduced in size, each weighing 125 Gm. The capsule stripped with some difficulty, leaving a slightly granular surface. On section, the cortex was somewhat diminished in size, and the markings were indistinct. The blood vessels were prominent. Microscopically, the cortex contained scattered patches of fibrosis, in which the glomeruli were changed into dense hyaline nodules. The larger vessels were sclerotic, and many of the arterioles showed hyaline deposits beneath the endothelium. A moderate round cell infiltration was present in the fibrotic areas. The pancreas, suprarenals and testicles were grossly normal. The skull was not opened.

*Anatomic Diagnosis*—A diagnosis was hemopericardium, ruptured aneurysm of the left coronary artery, coronary sclerosis, atherosclerosis and syphilitic meso-aortitis of the aorta, hypertrophy and dilatation of the left ventricle, dilatation of the right ventricle, pulmonary emphysema, fatty degeneration of the liver, chronic splenitis and renal arteriosclerosis.

#### SUMMARY

1 Aneurysm of the coronary arteries is an extreme rarity. This study is based on the records of twenty-nine cases gathered from the literature and one here reported.

2 The condition is three times as common in males as in females.

3 In the vast majority of cases the aneurysm is single and is usually situated on the left coronary artery within the first inch of its course.

4 Rupture of the aneurysm took place in 50 per cent of the cases.

5 Etiologically, the cases can be divided into two main groups: mycotic-embolic and arteriosclerotic.

6 The mycotic-embolic aneurysms occurred in association with an acute or subacute bacterial endocarditis of the aortic valve. The average age was 27.

7 In the arteriosclerotic group, a marked coronary sclerosis was present. The average age was 57.

8 Syphilitic meso-aortitis was found in only three cases in this series.

9 Trauma plays an insignificant etiologic rôle.

10 There were not any pathognomonic symptoms or physical signs which made possible an antemortem diagnosis of the condition.

# THE EFFECT OF ROENTGEN RAYS ON THE HEART

## II THE MICROSCOPIC CHANGES IN THE HEART MUSCLE OF RATS AND OF RABBITS FOLLOWING A SERIES OF EXPOSURES

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In a previous article,<sup>1</sup> we came to the conclusion that the single exposure of the precordium to roentgen rays of the quality and quantity described in that paper, and corresponding to a so-called human erythema dose, does not produce definite and irreparable injury to the heart muscles of adult rats and rabbits. The next step in these investigations suggested itself, i.e., the study of the effect of a series of exposures as they are carried out in the treatment of human beings. All malignant lesions in the region of the heart, for instance, mediastinal growth, carcinoma of the left breast, bronchus or a tumor of the lung are repeatedly treated at certain intervals with a single dose, varying from a part to a full tolerance dose. The latter term is used in preference to the "erythema dose," which implies a unit, but careful investigations have shown that it is not reproducible.<sup>2</sup>

### TECHNIC

The technical procedure was the same as in the previously reported experiments. Two types of radiation were used. In the first type the dosage was 200 kilovolts, 25 milliamperes, 40 cm. focal skin distance, 0.5 copper plus 1 aluminum filter, time of exposure, nine minutes,  $\lambda$  effective equaled 0.16 angstrom units in copper. The human skin tolerance dose was taken at 600 R as measured with the ionization chamber in air, representing, therefore, primary energy.<sup>3</sup> This value is called the roentgen value. In the second type of radiation, the dosage was 130 kilovolts, 5 milliamperes, 24 cm. focal skin distance, 4 aluminum filter,

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\* Submitted for publication, Aug. 16, 1928.

\* Read before the Section on Radiology at the Seventy-Ninth Annual Session of the American Medical Association, Minneapolis, June 14, 1928.

1 Warthin, A. S., and Pohle, E. A. The Effect of Roentgen Rays on the Heart. I. The Microscopic Changes in the Heart Muscle of Rats and Rabbits Following a Single Exposure, *J. A. M. A.* **89**:1825 (Nov. 26) 1927.

2 Pohle, E. A., and Barnes, J. M. Clinical and Physical Investigations of the Problem of Dosimetry in Roentgen Therapy, *Radiology* **10**:303, 1928.

3 As small fields were used, it may be assumed that the surface dose is identical with this value.

time of exposure, six minutes, lambda effective equaled 0.23 angstrom units in copper. The roentgen value was approximately 300 R. The figures given in the first paper for the roentgen value, namely, 1,100 R, should be corrected to about 660 R, because the discrepancy which existed at that time between the so-called German and the American unit has been removed, the two units are now identical.

In all our measurements of the output of the apparatus and tube, a Wulf ionometer calibrated in roentgen units served as an ionization instrument. Its sensitivity was checked by radium. The absolute standard for the roentgen unit was obtained by means of an open air ionization chamber in connection with a high sensitive galvanometer as suggested by Duane and Lorenz.<sup>4</sup>

Twenty-four rabbits and forty-eight rats, leaving two or three controls in each group of twelve animals, received treatment once a month for three months. The exposures were arranged so that an initial dose of 600 R over the precordium was followed by  $2 \times 300$  R in monthly intervals. In order to guarantee the correct position of the heart during the exposure, diagnostic films were taken in every case before treatment was begun (fig 1). The animals were killed from eight to thirty-two days after the last exposure, and the hearts were taken out and prepared for microscopic examination.

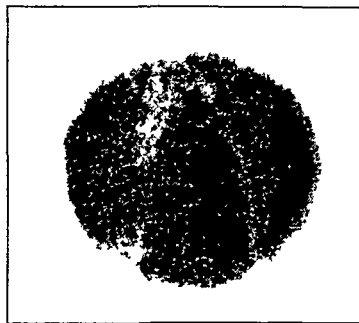


Fig 1—Roentgenogram of the heart taken before treatment

#### PROTOCOLS OF EXPERIMENTS

RAT 1 (series I, 4387-L-AF)—Killed 1-21-28. Well-marked Zenker's necrosis. Moderate fatty degenerative infiltration most marked beneath the epicardium. Endothelium of some of the smaller blood vessels showed swelling and vacuolation. The ganglion cells of the intracardiac nodes showed a well-marked chromatolysis. (Severe purulent bronchitis, particularly of the larger bronchi. Areas of purulent bronchopneumonia.)

RAT 2 (series I, 4379-L-AF)—Killed 1-21-28. Well-marked cloudy swelling and Zenker's necrosis. Fatty degenerative infiltration more marked than in rat 1, and particularly beneath the endocardium, but also well-marked beneath the epicardium. Changes more marked than in rat 1. Marked congestion of the small vessels and capillaries, particularly in the areas showing the most marked Zenker's necrosis. Pyknosis of many of the endothelial nuclei. Many nuclei of the valvular endocardium showed pyknosis. The ganglion cells of the intracardiac nodes showed a well-marked chromatolysis. (Severe purulent bronchitis, particularly of larger bronchi. Areas of purulent bronchopneumonia.)

4 Duane, W., and Lorenz, E. The Standard Ionization Chamber for Roentgen-Ray Dosage Measurements, *Am J Roentgenol* **19** 461, 1928.

5 Mr W. Thayer assisted in carrying out the animal experiments.

RAT 3 (series I, 4380-L-AF) —Killed 1-21-28 Changes similar in kind but to a much less marked degree as compared to rats 1 and 2 (Severe purulent bronchitis, particularly of the larger bronchi Areas of purulent bronchopneumonia)

RAT 4 (series I, 4381-L-AF) —Killed 1-21-28 Marked Zenker's necrosis Moderate fatty degenerative infiltration beneath epicardium and endocardium Numerous pyknotic endothelial nuclei No ganglion cells in sections examined (Severe purulent bronchitis, particularly of the larger bronchi Areas of purulent bronchopneumonia)

RAT 5 (series I, 4382-L-AF) —Killed 1-21-28 Marked Zenker's necrosis with fatty degenerative infiltration most marked on the endocardial side Numerous pyknotic endothelial nuclei In the adipose tissue at the base of the heart there were small areas of necrosis with inflammatory reaction Early localized epicarditis Ganglion cells showed marked chromatolysis (Severe purulent bronchitis, particularly of the larger bronchi Areas of purulent bronchopneumonia)

RAT 6 (series I, 4383-L-AF) —Killed 1-21-28 Well-marked Zenker's necrosis Fatty degenerative infiltration beneath epicardium and endocardium Scattered pyknotic nuclei Early epicarditis, localized toward the base Areas of inflammatory infiltration through the adipose tissue Degenerative changes in the ganglion cells (Severe purulent bronchitis, particularly of the larger bronchi Areas of purulent bronchopneumonia)

RAT 7 (series I, 4384-L-AF) —Killed 1-21-28 Moderate Zenker's necrosis Fatty degenerative infiltration Scattered pyknosis No ganglion cells in sections examined Ganglion cells showed the same degree of chromatolysis No epicarditis (Severe purulent bronchitis, particularly of the larger bronchi Purulent bronchopneumonia)

RAT 8 (series I, 385-L-AF) —Killed 1-21-28 Marked Zenker's necrosis, more so than in preceding protocol Numerous pyknotic endothelial and heart muscle nuclei Subepicardial and subendocardial fatty degenerative infiltration Slight increases of lymphocytes around some of the blood vessels Areas of marked Zenker's necrosis in the myocardium of the auricle Localized epicarditis Some degree of chromatolysis of ganglion cells as in the preceding protocol (Severe purulent bronchitis, particularly of the larger bronchi Areas of purulent bronchopneumonia)

RAT 9 (series I, 4386-L-AF) —Killed 1-21-28 Marked Zenker's necrosis particularly of the inner half of the left ventricle Fatty degenerative infiltration, both subendocardial and subepicardial Scattered pyknotic endothelial and myocardial nuclei Ganglion cells showed the same degree of chromatolysis Pyknotic nuclei observed in one nerve trunk Numerous large 'mast' cells in the adipose tissue about the ganglions (Severe purulent bronchitis, particularly of the larger bronchi Areas of purulent bronchopneumonia)

RAT 10 (series I, 4387-L-AF) —Control, killed 1-21-28 Early Zenker's necrosis and fatty degenerative infiltration, less marked than in preceding protocol Milder degree of bronchitis and bronchopneumonia

RAT 11 (series I, 4388-L-AF) —Control, killed 1-21-28 Changes similar to the preceding protocol, but less severe Early purulent bronchopneumonia

RAT 12 (series I, 4389-L-AF) —Control, killed 1-21-28 Well-marked Zenker's and fatty degenerative infiltration Numerous pyknotic nuclei Increase of interstitial nuclei in many areas Areas of fat necrosis at base of heart with beginning inflammatory reaction Early purulent mediastinitis

RAT 1 (series II, 4449-L-AF) —Killed 1-28-28 Well-marked Zenker's necrosis beneath the epicardium, more marked beneath the endocardium Numerous pyknotic nuclei Marked chromatolysis of ganglion cells (Purulent bronchitis of large bronchus)

RAT 2 (series II, 4450-L-AF) —Killed 1-28-28 Marked Zenker's necrosis Subepicardial and subendocardial fatty degenerative infiltration Many ganglion

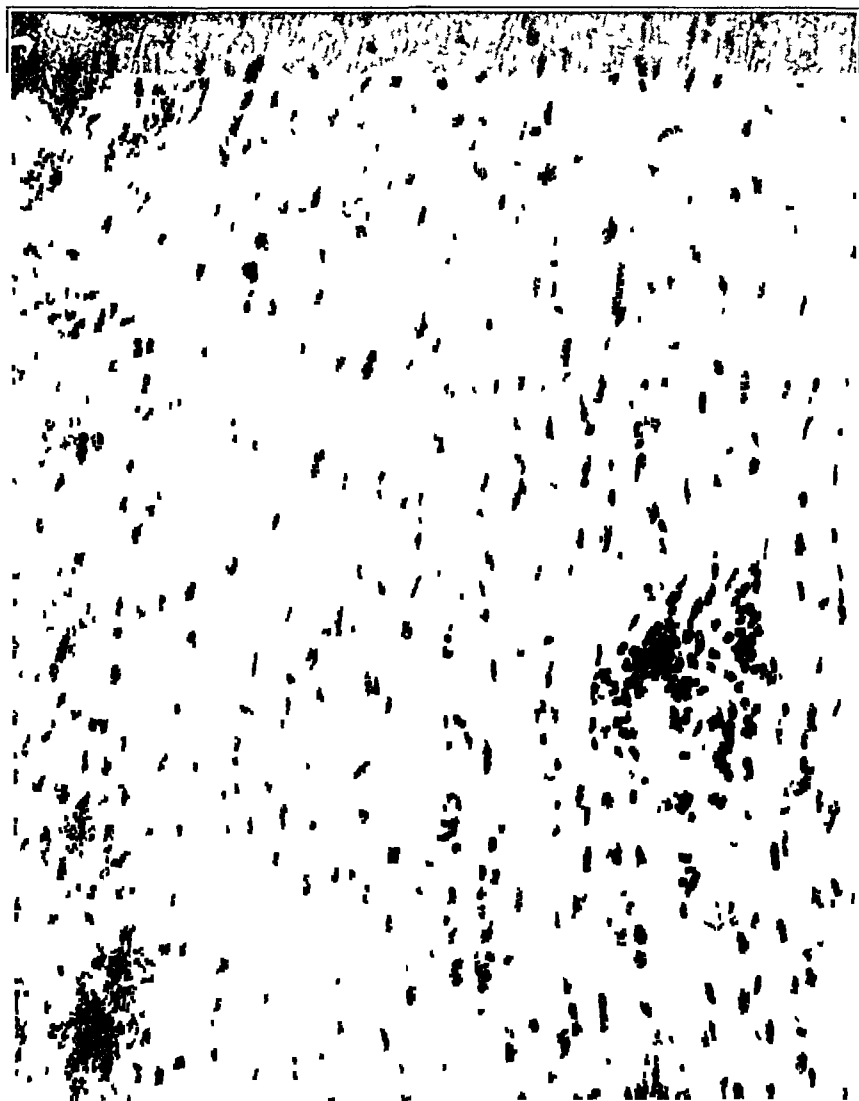


Fig 2 (series II rat 4) —Marked fatty degenerative infiltration and Zenker's necrosis of the muscle of the auricle and the right ventricle, marked Zenker's necrosis of the left ventricle

cells showed karyolysis and others showed marked chromatolysis (No lung tissue examined)

RAT 3 (series II 4451-L-AF) —Killed 1-28-28 Marked Zenker's necrosis Subepicardial and subendocardial fatty degenerative infiltration (Severe purulent bronchopneumonia) Edema of nerve trunks Chromatolysis of ganglion cells

RAT 4 (series II 4452-L-AF) —Killed 1-28-28 Marked fatty degenerative infiltration and Zenker's necrosis of muscle of auricle and right ventricle Marked

Zenker's necrosis of left ventricle Numerous pyknotic nuclei (Acute catarrhal bronchitis) Edema of large nerve trunk No ganglion cells included in sections examined

RAT 5 (series II, 4453-L-AF) —Killed 1-28-28 Ganglions showed marked chromatolysis Myocardium showed marked Zenker's necrosis and fatty degenerative infiltration most marked in auricle and right ventricle (Acute catarrhal bronchitis)

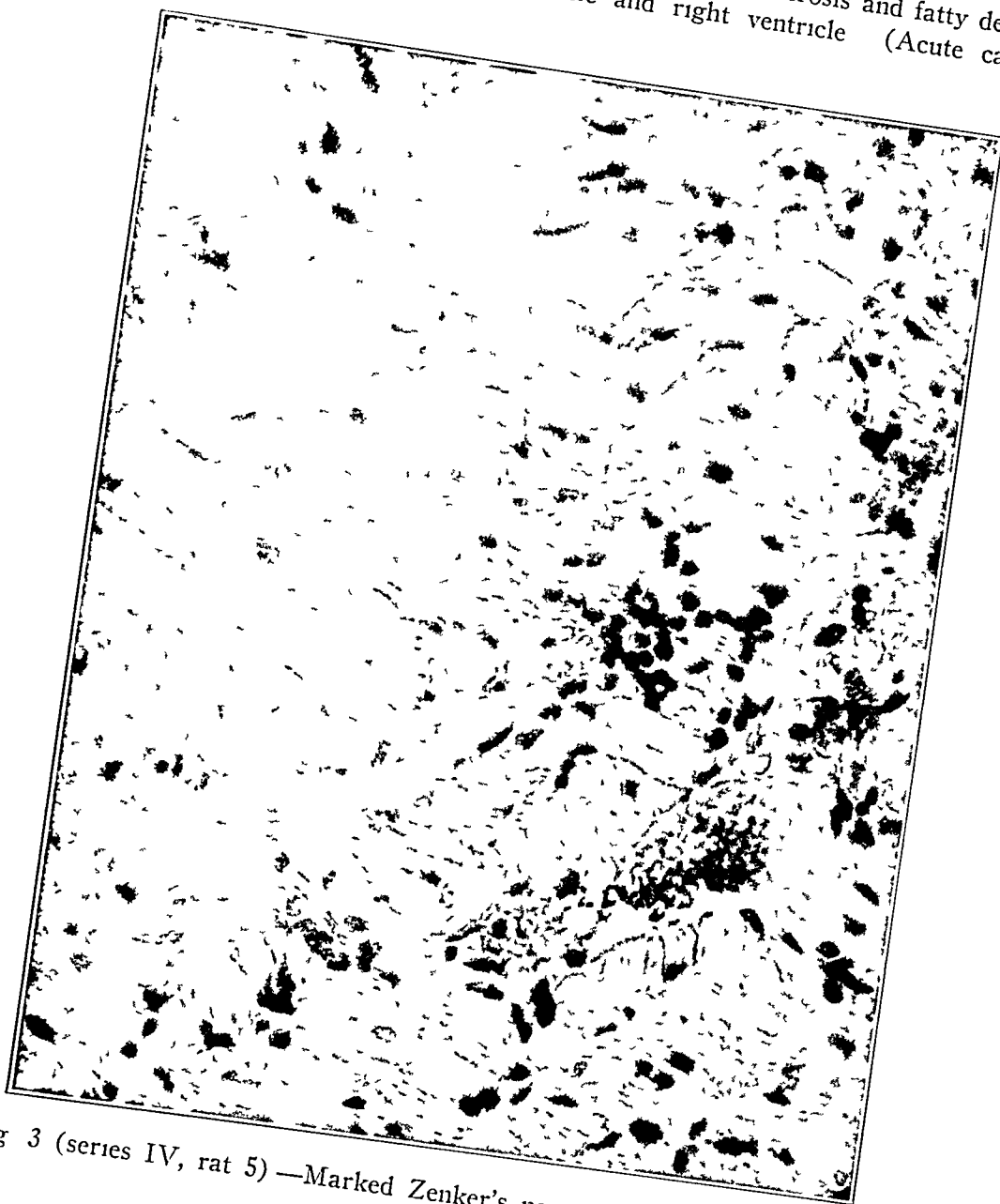


Fig 3 (series IV, rat 5) —Marked Zenker's necrosis, small areas of pyknotic nuclei

RAT 6 (series II, 4454-L-AF) —Killed 1-28-28 Well-marked Zenker's necrosis Fatty degenerative infiltration Edema of nerve trunks Chromatolysis of ganglion cells (Very severe purulent bronchitis and bronchopneumonia) Early epicarditis, Small areas of interstitial myocarditis

RAT 7 (series II, 4455-L-AF) —Killed 1-28-28 Marked Zenker's necrosis Subepicardial and subendocardial fatty degenerative infiltration Pyknosis of nuclei Increase of interstitial cells in heart muscle Marked edema and degeneration of large nerve trunks Chromatolysis of ganglion cells



RAT 8 (series II, 4456-L-AF) —Killed 1-28-28 Marked Zenker's necrosis Subendocardial fatty degenerative infiltration Marked fatty degenerative infiltration of right auricle and right ventricle Marked chromatolysis of ganglion cells Complete destruction of nuclei (Purulent bronchopneumonia) Lymph nodes largely replaced by cells resembling myelocytes or plasma cells In the sinuses of the nodes large basophilic reticulo-endothelial cells

RAT 9 (series II, 4457-L-AF) —Killed 1-28-28 Marked Zenker's necrosis Subepicardial and subendocardial fatty degenerative infiltration, more marked in

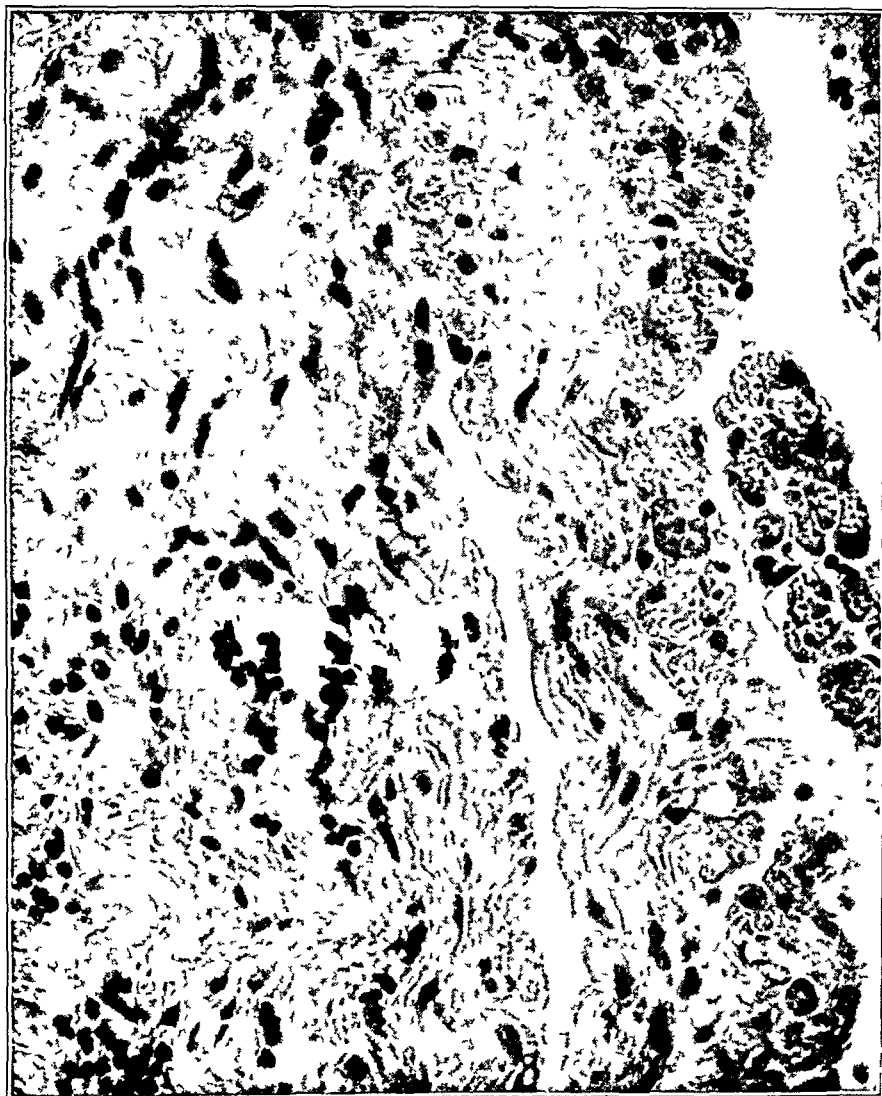


Fig 4 (series I, rat 4) —Marked Zenker's necrosis, moderate fatty degenerative infiltration beneath epicardium and endocardium

right ventricle than in the left Acute epicarditis Chromatolysis of ganglion cells (Purulent bronchopneumonia)

RAT 10 (series II, 4458-L-AF) —Died 1-12-28 Marked Zenker's necrosis Fatty degenerative infiltration both subepicardial and subendocardial Localized increase of interstitial nuclei (No lung tissue included) No ganglions found in sections examined

RAT 11 (series II, 4459-L-AF) —Control, killed 1-28-28 (Purulent broncho-pneumonia) Marked Zenker's necrosis Subepicardial and subendocardial fatty degenerative infiltration Edema of nerve trunks Early pleuritis Chromatolysis of ganglion cells

RABBIT 1 (series I, 6093-L-AF) —Died 3-4-28 Marked Zenker's and simple necrosis without inflammatory reaction Large red thrombus in left ventricle Suffusion with hemoglobin (post mortem?) No pneumonia Catarrhal bronchitis

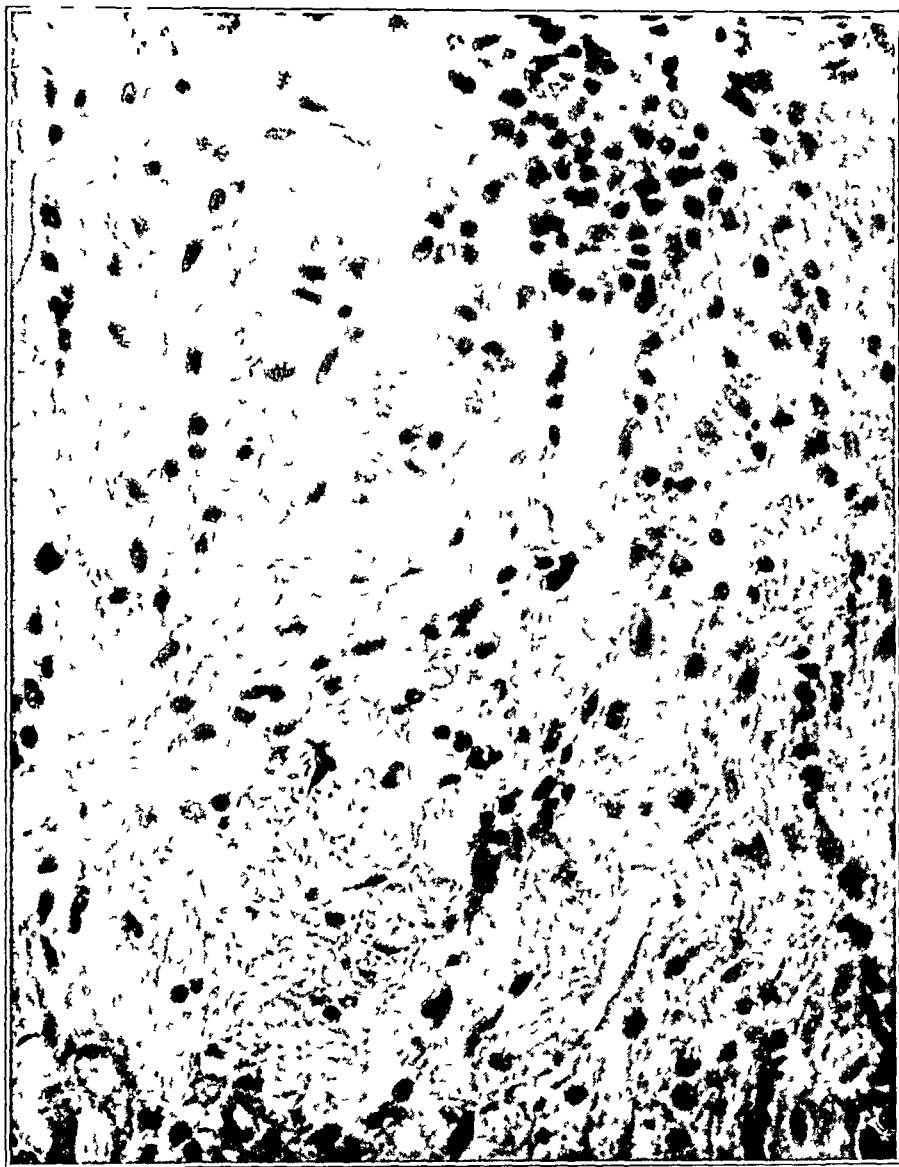


Fig 5 (series I, rat 5) —Marked Zenker's necrosis with fatty degenerative infiltration most marked on the endocardial side

of the larger bronchi Hyperplasia of the reticulo-endothelium of the bronchial lymph nodes

RABBIT 3 (series I, 6094-L-AF) —Killed 3-22-28 Moderate Zenker's necrosis Marked fatty degenerative infiltration beneath endocardium, particularly of the papillary muscles Pyknosis of interstitial nuclei Some localized increase of interstitial nuclei Small areas of definite interstitial myocarditis in muscle near base of heart Fatty change is more marked in the auricular wall than elsewhere Catarrhal bronchitis

RABBIT 4 (series I, 6095-L-AF) —Killed 3-22-28 Zenker's necrosis and marked fatty degenerative infiltration Localized increase of the interstitial nuclei Marked lipoidosis of endocardium of aortic valve There were areas scattered throughout the wall of the heart of definite interstitial inflammation and repair of focal necrosis Endocardium near these areas showed a marked lipoidosis Nerve trunks showed no change Early epicarditis No ganglions found Catarrhal bronchitis

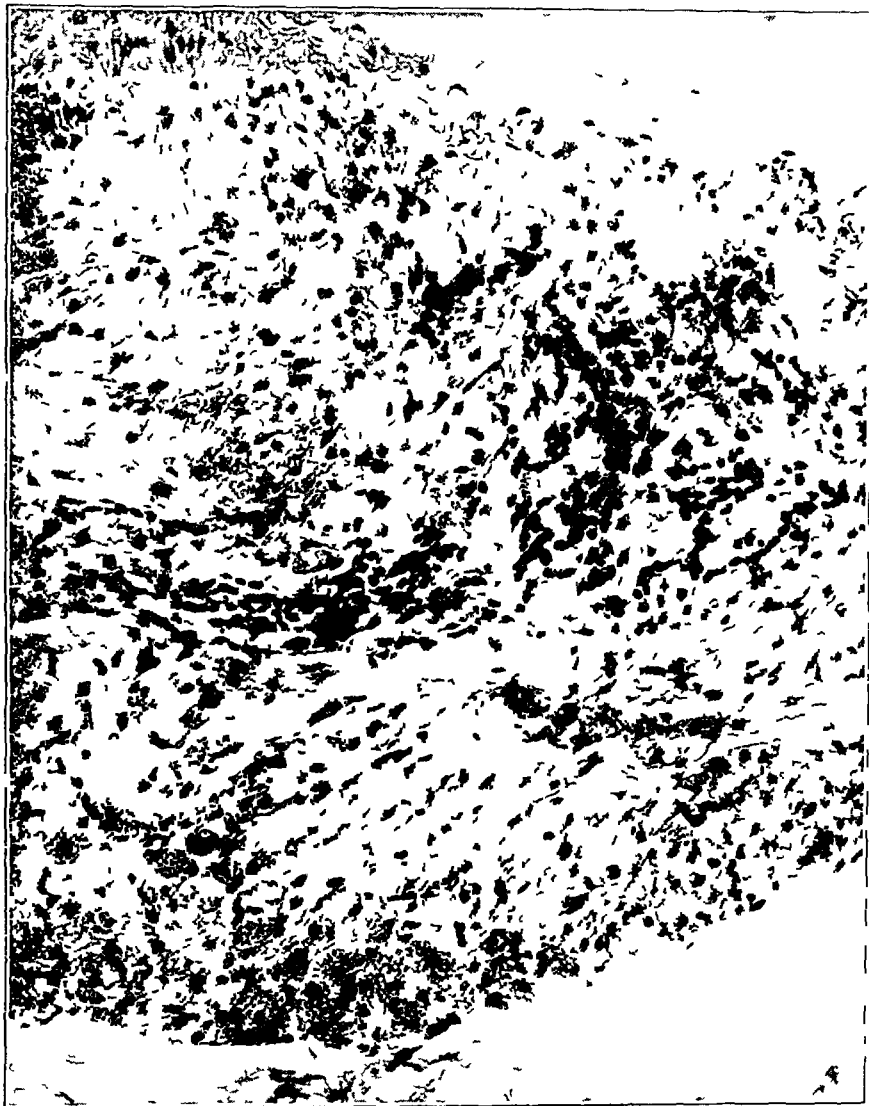


Fig 6 (series I, rat 6) —Well-marked Zenker's necrosis, fatty degenerative infiltration beneath epicardium and endocardium

RABBIT 5 (series I, 6096-L-AF) —Killed 3-22-28 Zenker's necrosis Marked subendocardial fatty degenerative infiltration Numerous pyknotic interstitial nuclei Small areas of small-celled infiltration, more marked in the auricular walls than in the ventricle Focal areas of complete necrosis of heart muscle with beginning repair No ganglions found Catarrhal bronchitis in main trunks

RABBIT 6 (series I, 6097-L-AF) —Killed 3-22-28 Zenker's necrosis Diffuse fatty degenerative infiltration, more marked beneath the endocardium and in the

papillary muscles Numerous small areas of increased interstitial nuclei, lymphocyte infiltration Some of these areas showed pyknotic nuclei Nerve trunks negative Definite inflammatory infiltrations in auricular wall Auricular ganglion showed marked chromatolysis Catarrhal bronchitis

RABBIT 7 (series I, 6098-L-AF) —Killed 3-22-28 Marked Zenker's necrosis Fatty degenerative infiltration most marked beneath the endocardium Small areas

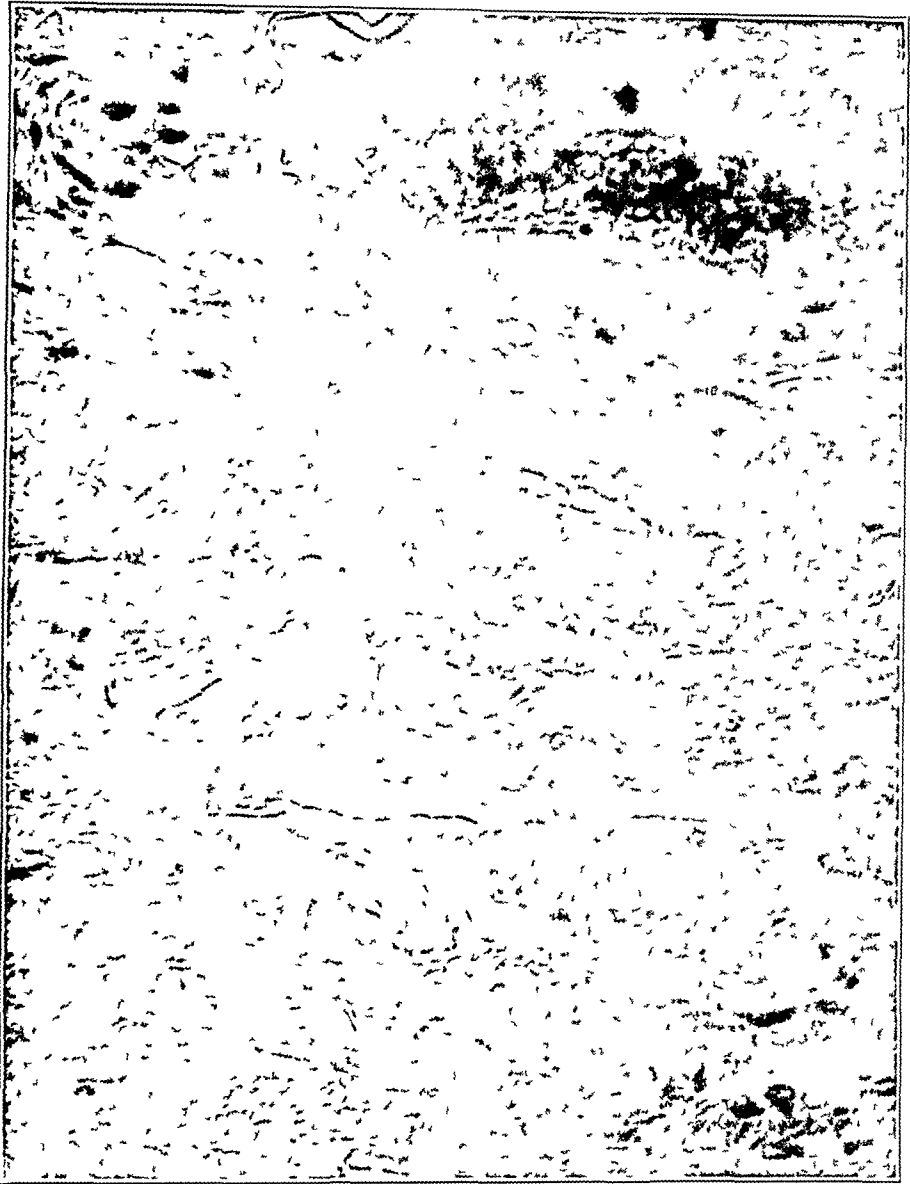


Fig 7 (series III, rat 2) —Extreme Zenker's necrosis

of lymphocyte infiltration and increase of interstitial nuclei No ganglion found Nerve trunks negative Catarrhal bronchitis in large bronchi

RABBIT 8 (series I, 6099-L-AF) —Died 2-24-28 Marked Zenker's necrosis and fatty degenerative infiltration, but few normal muscle fibers Very slight increase of interstitial nuclei Auricular wall showed marked fatty degenerative infiltration Catarrhal bronchitis in large bronchi

RABBIT 9 (series I, 6100-L-AF) —Killed 3-22-28 Marked Zenker's necrosis and fatty degenerative infiltration Very small aggregations of lymphocytes and

interstitial nuclei Nerve trunks showed no changes except that one has a lymphocytic infiltration along its intraneural blood vessel No ganglion found Catarrhal bronchitis

RABBIT 10 (series I, 6101-L-AF) —Killed 3-22-28 Marked Zenker's necrosis and fatty degenerative infiltration Localized increase of interstitial nuclei Numerous small lymphocyte infiltrations Changes most marked in auricle and wall of ventricle Large areas of marked Zenker's necrosis in wall of right

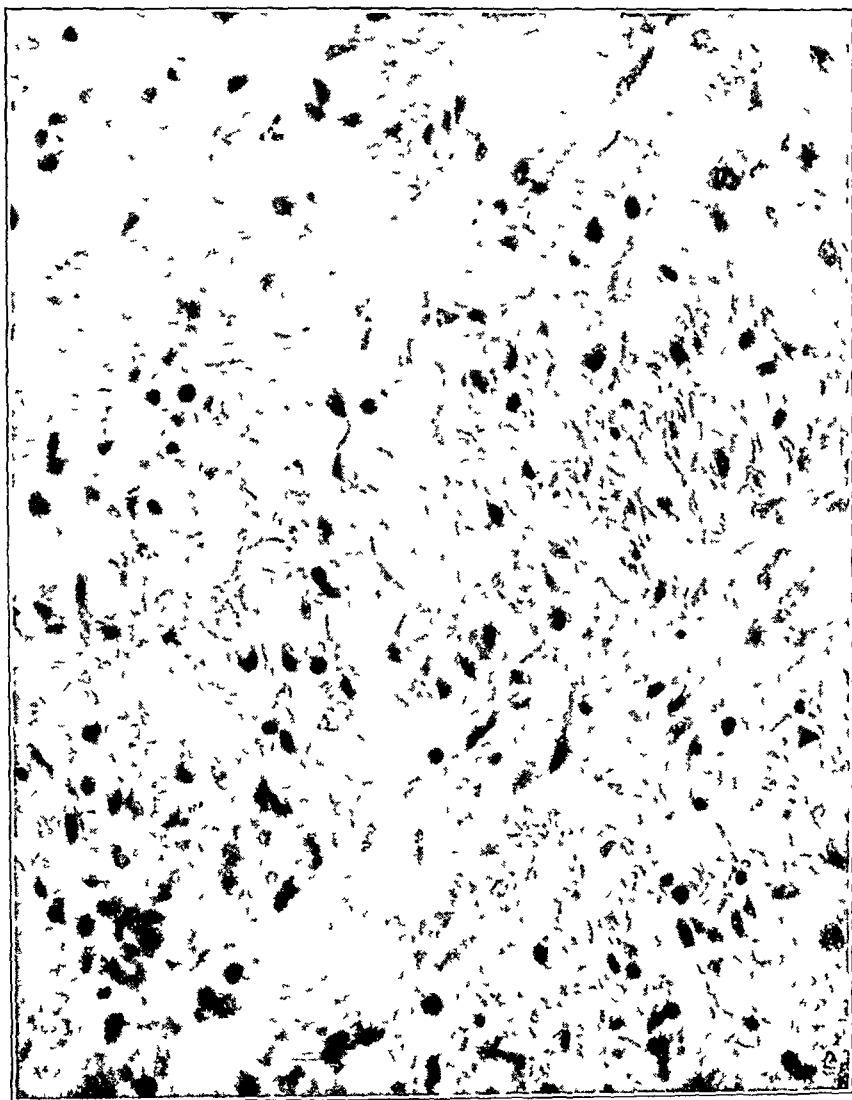


Fig 8 (series I, rabbit 4) —Zenker's necrosis and marked fatty degenerative infiltration

auricle and ventricle Early inflammatory reaction and some repair No ganglions found Purulent catarrh of large bronchi

RABBIT 11 (series I, 6091-L-AF) —Control, killed 3-22-28 No Zenker's necrosis Heart showed fatty infiltration and a diffuse fatty degenerative infiltration Early atherosclerosis of aorta No pneumonia

RABBIT 12 (series I, 6092-L-AF) —Control, killed 3-22-28 No Zenker's necrosis Diffuse fatty degenerative infiltration, more marked beneath the endocar-

dium Subepicardial fatty infiltration Slight lipoidosis of intima of aorta (Nodules of cartilage in the aortic valve Old atherosclerosis of this valve) No pneumonia

RAT 1 (series III, 7004-L-AF) —Died 3-5-28 Extreme Zenker's necrosis of heart muscle (Multiple abscesses in lung Caseation of pus Purulent bronchopneumonia)

RAT 2 (series III, 7007-L-AF) —Killed 5-2-28 Extreme Zenker's necrosis No reactions

RAT 3 (series III, 7005-L-AF) —Died 4-18-28 Extreme Zenker's necrosis Very little fatty degenerative infiltration No reactions Necrosis of ganglion cells Purulent bronchopneumonia

RAT 4 (series III, 7009-L-AF) —Died 4-30-28 Marked Zenker's necrosis Parietal mixed thrombus with karyorrhexis of the leukocyte nuclei Marked chromatolysis of the ganglion cells In the cardiac thrombus many colonies of bacteria Thrombo-endocarditis purulenta The thrombus rests on a completely necrotic endocardium and myocardium

RAT 5 (series III, 7008-L-AF) —Killed 5-2-28 Marked Zenker's necrosis, slightly less marked than in the preceding protocol No reactions Catarrhal bronchitis

RAT 6 (series III, 7006-L-AF) —Died 4-25-28 Extreme Zenker's necrosis Marked necrosis of ganglion cells No reactions Purulent bronchopneumonia

RAT 7 (series III, 7010-L-AF) —Killed 5-2-28 Moderate Zenker's necrosis No reaction Catarrhal bronchitis

RAT 8 (series III, 7011-L-AF) —Killed 5-2-28 Marked Zenker's necrosis No reactions

RAT 9 (series III, 7012-L-AF) —Killed 5-2-28 Marked Zenker's necrosis No reactions (Diffuse purulent pneumonia)

RAT 10 (series III, 7013-L-AF) —Control, killed 5-2-28 Marked Zenker's necrosis Small localized increase of stroma cells No ganglion found Purulent bronchopneumonia

RAT 11 (series III, 7014-L-AF) —Control, killed 5-2-28 Same as preceding protocol

RAT 12 (series III, 7015-L-AF) —Control, killed 5-2-28 Marked Zenker's necrosis Small localized areas of inflammation Chromatolysis of ganglion cells Purulent bronchopneumonia

RAT 1 (series IV, 7016-L-AF) —Killed 5-2-28 Marked Zenker's necrosis No reaction No pneumonia

RAT 2 (series IV, 7017-L-AF) —Killed 5-2-28 Marked Zenker's necrosis Chromatolysis of ganglion cells No reactions No pneumonia

RAT 3 (series IV, 7018-L-AF) —Killed 5-2-28 Marked Zenker's necrosis Marked edema of nerve trunks Marked chromatolysis of ganglion cells No reactions No pneumonia

RAT 4 (series IV, 7019-L-AF) —Killed 5-2-28 Marked Zenker's necrosis No reactions Catarrhal pneumonia

RAT 5 (series IV, 7020-L-AF) —Killed 5-2-28 Marked Zenker's necrosis Small areas of pyknotic nuclei (Small areas of pneumonia) No reactions Ganglion cells not found

RAT 6 (series IV, 7021-L-AF) —Killed 5-2-28 Marked Zenker's necrosis No reactions (Acute catarrhal bronchitis)

RAT 7 (series IV, 7022-L-AF) —Killed 5-2-28 Marked Zenker's necrosis  
Small areas of pyknotic nuclei and lymphocyte infiltration No pneumonia

RAT 8 (series IV, 7023-L-AF) —Killed 4-30-28 (Severe necrotic hemorrhagic pneumonia) Marked Zenker's necrosis of myocardium (Marked purulent bronchitis of larger bronchi Purulent mediastinitis) Very marked necrosis of auricular wall



Fig 9 (series I, rabbit 6) —Zenker's necrosis, diffuse fatty degenerative infiltration, more marked beneath the endocardium and in the papillary muscles

RAT 9 (series IV, 7024-L-AF) —Killed 5-2-28 Marked Zenker's necrosis  
A few small reactions No ganglions found Catarrhal bronchitis

RAT 10 (series IV, 7025-L-AF) —Control, killed 5-2-28 Zenker's necrosis  
less marked than in preceding protocol No reactions Catarrhal bronchitis

RAT 11 (series IV, 7026-L-AF) —Control, killed 5-2-28 Marked Zenker's  
necrosis No reactions Purulent bronchopneumonia

RAT 12 (series IV, 7027-L-AF) —Control, killed 5-2-28 Well-marked  
Zenker's necrosis No reactions Bronchopneumonia

# WARTHIN-POHLE—ROENTGEN RAYS ON THE HEART 27

RABBIT 1 (series II 7137-L-AF) —Killed 5-15-28 Moderate Zenker's necrosis with diffuse fatty degenerative infiltration Nerve trunks negative Ganglions not found No reactions No pneumonia

RABBIT 2 (series II 7138-L-AF) —Killed 5-15-28 Diffuse fatty degenerative infiltrations Very slight Zenker's necrosis Endocardial thickenings with myxomatous change No pneumonia

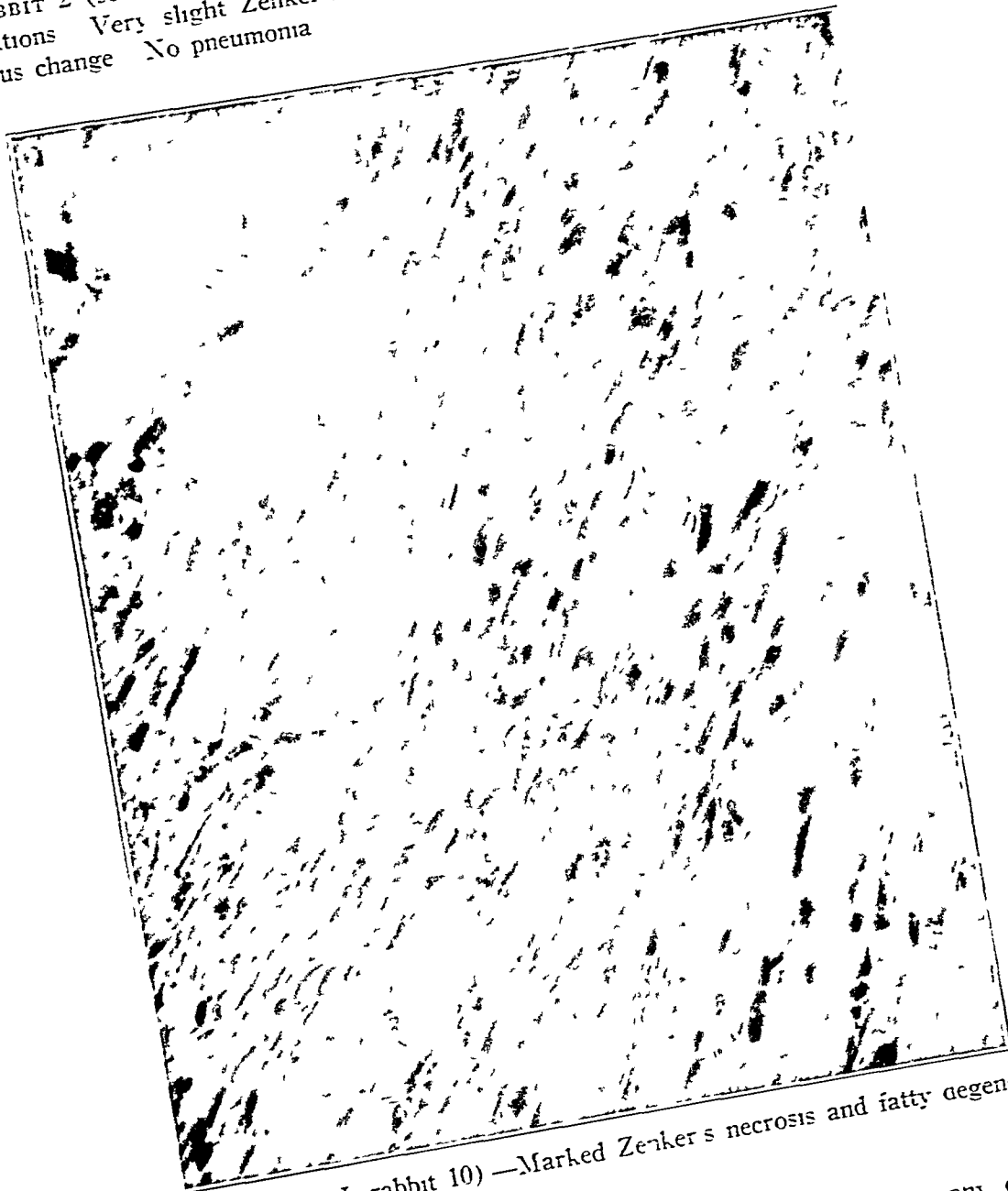


Fig 10 (series I rabbit 10) —Marked Zenker's necrosis and fatty degenerative infiltration

RABBIT 3 (series II 7139-L-AF) —Died 3-27-28 Marked atrophy of heart muscle Relative increase of stroma and nuclei Myxomatous thickening of endocardium Marked serous atrophy of subpericardial fat Fatty degenerative infiltration but no Zenker's necrosis No pneumonia

RABBIT 4 (series II, 7140-L-AF) —Killed 5-15-28 Atrophy of heart muscle Well-marked Zenker's necrosis Fatty degenerative infiltration most marked beneath the endocardium Large areas of well-marked myocarditis Increase of interstitial nuclei throughout Catarrhal bronchitis in large bronchi



RABBIT 5 (series II, 7141-L-AF) —Killed 5-15-28 Atrophy with relative increase of stroma nuclei Subepicardial and subendocardial fatty degenerative infiltration Small inflammatory reactions Myxomatous thickening of endocardium Catarrhal bronchitis in large bronchi

RABBIT 6 (series II, 7142-L-AF) —Killed 5-15-28 Atrophy Zenker's necrosis Fatty degenerative infiltration, most marked beneath the endocardium

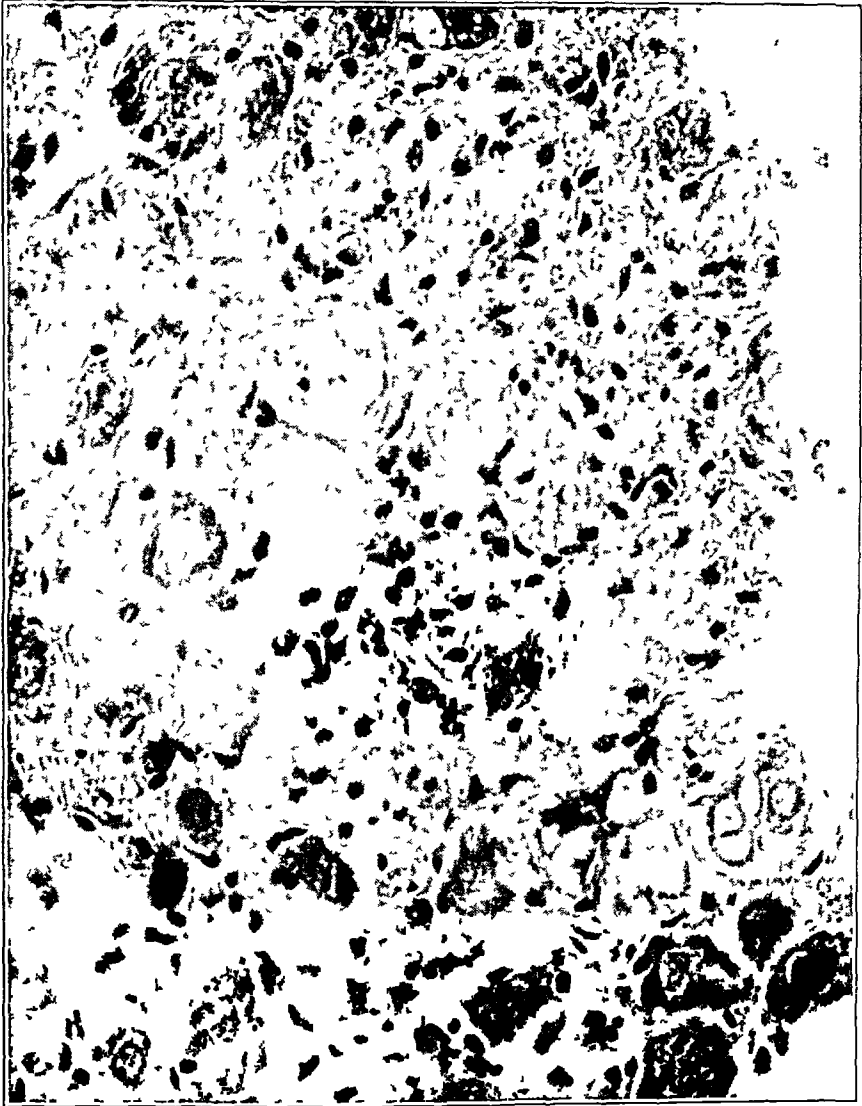


Fig 11 (series III, rat 6) —Extreme Zenker's necrosis, marked necrosis of ganglion cells

Increase of stroma nuclei Small areas of inflammatory infiltrations Acute purulent epicarditis Marked atrophy of thymus Myxomatous thickening of endocardium Localized perivascular infiltrations Purulent bronchitis

RABBIT 8 (series II, 7143-L-AF) —Killed 5-15-28 Zenker's necrosis Diffuse fatty degenerative infiltration most marked beneath the endocardium Localized increase of nuclei and small lymphocyte infiltrations Marked thymic atrophy Catarrhal bronchitis in large bronchi

RABBIT 10 (series II, 7144-L-AF) —Control, killed 5-15-28 Atrophy Zenker's necrosis Fatty degenerative infiltration, most marked beneath the endocardium Increase of stroma Localized inflammatory infiltrations Characteristic of "rabbit encephalitis"

RABBIT 11 (series II, 7145-L-AF) —Control, killed 5-15-28 Abnormal Atrophy Zenker's necrosis Subendocardial fatty degenerative infiltration, marked in the papillary muscles Relative increase of stroma cells Small lymphocyte infiltrations (Rabbit encephalitis?)

RABBIT 12 (series II, 7146-L-AF) —Control, killed 5-15-28 Marked Zenker's necrosis Fatty degenerative infiltration, most marked beneath the endocardium Relative increase of stroma Small lymphocyte infiltrations Nerve trunks are negative No ganglion cells found Acute epicarditis (Purulent bronchopneumonia) Coronary vessels showed some sclerosis (Encephalitis?)

#### COMMENT ON PATHOLOGIC CHANGES CAUSED BY THE ROENTGEN RAYS

All of the irradiated animals (rats and rabbits) of these series showed marked myocardial lesions. The lesions consisted essentially in more severe degrees of Zenker's hyaline degeneration and necrosis and of fatty degenerative infiltration (lipoidosis) than were observed in the animals described in our first paper as following a single exposure. Furthermore many of the animals showed varying degrees of inflammatory reactions and beginning interstitial proliferation. In general, the pathologic changes in the myocardium observed in these animals can be compared with lesions seen in the human heart in moderately severe and in severe diphtheria toxemia.

The exact interpretation of these lesions, so far as their production by irradiation is concerned, is rendered difficult by the complicating occurrence of a more or less severe purulent or catarrhal bronchitis and bronchopneumonia. The main bronchial trunks and the portions of the lungs in the anterior mediastinum were especially involved. The severity of these pulmonary lesions varied from a catarrhal bronchopneumonia to the occurrence of multiple pulmonary abscesses. There were also associated varying degrees of local or generalized mediastinitis, early pericarditis and pleuritis. In two of the animals (rat 4, series III and rabbit 1, series I), there was also a thrombo-endocarditis present. Bacterial colonies were seen in all of the lesions, so that there is no doubt as to the ultimate infective nature of these processes. Unfortunately, similar pulmonary lesions were found in the majority of the controls, and in some of these the same type of myocardial lesions of a less severe degree, with the exception of two cases among the control rats (series II, rat 11, series IV, rat 11) and in three control rabbits (series II, rabbits 10, 11 and 12). In addition to the pulmonary infection, these three animals showed myocardial lesions common to "rabbit encephalitis". With this complication, it becomes difficult to evaluate the actual rôle of irradiation in contributing to the myocardial damage. As some of the animals (control rats, series IV, rats 10 and 12, series I,

rats 10 and 11, and control rabbits, series I, rabbits 11 and 12) showed much milder myocardial lesions in spite of the associated pulmonary involvement, and because the controls with bronchopneumonia and myocardial lesions usually presented milder degrees of the latter it seems safe to conclude that the heart lesions, in large measure at least were due to the irradiation. This deduction is more safely drawn concerning the rats than concerning the rabbits because of the complicating heart lesions of rabbit encephalitis found in the rabbit controls. For this reason we regard the rabbit as highly unsuitable for this especial research. It seems that the great majority of laboratory rabbits obtained at the University of Michigan show spontaneous myocardial lesions. The focal lymphocytic character of these lesions however can be used as a differential point in evaluating myocardial change due to other factors.

Carefully weighing the evidence we feel that we are justified in concluding that the exposures given to these animals produced a primary mediastinal injury involving the heart, large bronchi, portions of the lungs, lymph nodes, thymus and ganglions. As a result of this primary injury an infective bronchitis and bronchopneumonia followed in every exposed subject frequently extending to pleurae, mediastinum and pericardium and in two cases associated with hematogenous bacterial thrombo-endocarditis. The lymph nodes and thymus of the region showed evidence of lymphoid destruction and reticulo-endothelial hyperplasia, areas of fat necrosis were present in the mediastinal fat, and the ganglions of the region showed marked chromatolysis and lipoidosis. Many nerve trunks were markedly edematous, and some showed lipoidosis. Some of these lesions did not have any relationship to the pneumonia and were not due to infection. They occurred only in the irradiated animals. The changes common to infection were as a rule much more severe in the irradiated animals than in the controls dying with the severest form of pulmonary infection, even when in the rabbit controls associated with the lesions of rabbit encephalitis.

Although our animals were most carefully selected and were kept under the very best conditions, a bronchial and pulmonary infection was practically universal among them. It seems probable that this began in the irradiated animals. As the result of the irradiation, the bronchi are damaged, then resistance lowered, and an infective bronchitis and bronchopneumonia developed. This in turn will increase the damage already produced by the irradiation in the myocardium and the combination is sufficient to cause the spontaneous death of some animals. Since the controls were kept with the irradiated animals the conditions favored the spread of the infection to them from the latter. This fact is of great importance. The main bronchial trunks are injured in mediastinal irradiation (repeated exposures) to such a degree that secondary pulmonary infection almost invariably results. To the pri-

myocardial injury is added the possibility of increased toxic injury and mechanical strain on the heart. The secondary infection may extend directly to the pericardium and heart, or the latter may be involved by hematogenous infection of the endocardium (thrombo-endocarditis). The injury to the nervous apparatus (ganglions) must cause added embarrassment to the circulation.

Comparing these observations with those of Hartman, Bolliger, Doub, and Smith,<sup>6</sup> we confirm their conclusion as to the possibility of injury to the myocardium by roentgen rays of short wave length. Unfortunately, no direct comparison of these two investigations is possible, since the foregoing authors did not make exact measurements of the applied dose. From an approximate estimate of the energy used by them, it would appear that the smallest exposure given by them must have been a multiple of our tolerance dose. There is no doubt that a dose of that order of magnitude must have a destructive effect on living tissue. As far as the human cases reported by them are concerned, no dose can be computed from the data given in the report, and the pathologic observations are not conclusively differentiated. There is no positive proof that the myocardial lesions were due to the irradiation. As far as our own clinical experience is concerned, no roentgen-ray injury of the heart was observed at autopsy in patients who had been treated over the precordium.

That an overdose of radium can lead to necrosis of the myocardium has been shown recently by E. Renfer.<sup>7</sup> In two cases of esophageal carcinoma in which treatment by radium was used (1968 and 2160 mgh), he observed deep necrosis of the myocardium, in one case leading to rupture of the left ventricle and hemopericardium, with a latent period of from five to six months.

As Levy and Golden<sup>8</sup> have attempted to treat persons with heart disease (rheumatic carditis), the foregoing investigations should be borne in mind when dosage for an exposure which would place the heart in the path of the irradiation is prescribed.

#### CONCLUSIONS

1 The precordium of forty-eight rats and twenty-four rabbits (leaving two or three in each group of twelve animals as controls) was exposed to roentgen rays ( $\lambda$ -effective equaled 0.16 and 0.23

6 Hartman, F., Bollinger, A., Doub, H., and Smith, J. Heart Lesions Produced by the Deep X-Ray. An Experimental and Clinical Study, *Bull. Johns Hopkins Hosp.* **41** 36, 1927.

7 Renfer, E. Ueber zwei Falle von Radiumnekrosen des Myokardes, *Le cancer*, 1927, Jg. 4, 431, quoted from *Zentralbl. f. ges. Radiol.* **4** 586, 1928.

8 Levy, R., and Golden, R. Some Effects of Roentgen Irradiation of the Heart in Rheumatic Carditis, *Am. J. Roentgenol.* **18** 103, 1927.

angstrom units, respectively) three times at monthly intervals. The dose amounted to 600 R the first time and 300 R each the second and third time. The animals were killed from eight to thirty-two days following the last exposure and the hearts examined microscopically.

2 In every animal irradiated, definite lesions were found in the myocardium consisting essentially of marked Zenker's necrosis and fatty degenerative infiltration. In many cases there was evidence of inflammatory reaction and early repair. These myocardial lesions were associated in every irradiated animal with a more or less severe bronchitis and bronchopneumonia and with other evidences of mediastinal roentgen-ray injury to the thymus, lymph nodes and ganglions. We regard the pulmonary infection as secondary to the irradiation injury of the bronchi, lowering the resistance and being followed by secondary bacterial infection. A vicious circle is therefore set up increasing the myocardial change.

3 We conclude, therefore from these investigations that definite injury of the heart muscle results from a series of exposures as described. This suggests caution in any case in which the treatment brings the heart in the path of the rays.

4 An attempt will be made to define the threshold value of roentgen-ray energy for the lesions described, or in other words, the tolerance dose for the heart muscle.

#### ABSTRACT OF DISCUSSION

DR FRANK W. HARTMAN, Detroit. Our work was done with the purpose of producing an experimental heart lesion. I am very glad that Dr. Warthin and Dr. Pohle have been able to confirm our results on animals. Our first work was done at about the same time that Dr. Warthin and Dr. Pohle started theirs. As to the apparatus and dosage, we used relatively large doses, but the apparatus was carefully calibrated. In fact, Dr. Pohle calibrated our apparatus. The dosage was carefully controlled—the distance, voltage, amperage and everything, except the ionization chamber which Dr. Pohle mentioned, was taken into account. The doses were unusually large because we started out to produce an experimental lesion so that we might study the irregularities in the heart following these permanent lesions. As to the experiments reported by Dr. Pohle, it seems to me that the presence of so much infection would largely obviate the possibility of definite conclusions. We used dogs rather than rats and rabbits, and in only one case did we see any evidence of infection in the heart or pericardium. This animal had a bacterial endocarditis and a septicemia. With this exception, the changes reported by us may be accepted as being due to the roentgen ray. As to cases in human beings, Dr. Warthin will possibly feel differently about them after he has reviewed the original sections made from the hearts. Many of you saw our demonstration last year in which three cases in human beings were presented. Since that time we have seen another. All of these were cases of mediastinal tumor and large doses of irradiation were given ranging from 60 to 200 minutes with the same voltage, amperage, filterage and distance used in our experimental work. I am not enough of a physicist or radiologist to tell you how that can be compared with

the dosage described by Dr Pohle, but I do know that it is well within the limits of dosage used for malignancy of the mediastinum. If you recall some of the high power photomicrographs of the myocardium as shown in the demonstration last year you will remember that about every other muscle fiber appeared as a hollow tube the center of which was filled with large vacuoles or occasionally a single coagulated mass of protoplasm. I do not think that anybody would deny that such a lesion is produced by the roentgen ray. Similar marked changes in human beings have been described by German authors, particularly by Schweitzer.

There is another phase of the work that I should like to emphasize and that is the fallacy of applying results obtained on one animal to other animals or to man. We reported lesions produced in dogs, sheep and human beings. We found that the dogs are much more susceptible than sheep, and dogs are somewhat more susceptible than man. As Davis pointed out several years ago, the right auricle in the dog is particularly susceptible, and even with moderate doses projected through the wall of the chest, lesions are produced. Davis did this work while he was showing clinical changes in the lung. In the sheep it is entirely different. You can project as much as 300 minutes of the dosage, such as Dr Pohle has mentioned through the anterior aspect and side of the chest in sheep, and you will not get any such hemorrhagic lesions. We do not see these hemorrhagic lesions in man either, but the sheep die just the same from myocardial degeneration and some of the most marked instances of necrosis and polymorphonuclear infiltration were shown in these sheep. There is also a large variability between individual animals. I do not think this is accounted for by difference in the contour of the chest or from difference in roentgen technic, but there is a large difference in susceptibility. I have no doubt that men with large experience have seen the same thing in human patients. One other thing is the possibility of controlling the effects in human beings with the electrocardiograph. We have been able to do that satisfactorily in our dogs and sheep, and in the last year we have been following up by means of the electrocardiograph every case in which irradiation was given over the chest. We have been able to show that when the voltage becomes low or when the T waves become inverted, the myocardium is suffering and it is time to rest a while.

DR G E PRAHLER Philadelphia. We must especially emphasize the point brought out by Dr Hartman, namely that need for caution in transferring data obtained in the treatment of experimental work on small animals to man. Take the size of the animals. Judging by the diagrams shown by Dr Pohle, at least three fourths of the animal's chest was exposed, and about one third of the entire body. Then we give this small animal the doses we would give to a human being! We go a step further, according to this technic, and give a full dose of roentgen rays to this animal, a massive dose, which I think none of us do at the present time, and then he repeats that in one month, and again in another month. I know of no one who repeats a massive dose inside of two months in a human case. Therefore, we must conclude that relatively this animal received at least ten times the relative dosage that would be given to a human being. The results obtained in this experimental work are inconsistent with the clinical observations all of us have made. I have treated over 1,000 patients with carcinoma of the breast which involved more or less exposure of the heart. I have never seen any clinical symptoms to indicate that the heart was affected. I have performed many autopsies and no such results have been reported as have been indicated in this experimental work. Within the past year we had a very complete autopsy in a case of Hodgkin's disease. I had treated the patient in 1920. There was a large mass about twice the size of the heart in the mediastinum.

This mass completely disappeared under radiation, and, of course, we had to treat the heart. The patient finally died of the disease, and at autopsy, Hodgkin's lesions were found in all the tissues of the body, including the heart, and yet there were no such results reported as we find in this case. The animal experiments shown had associated a pneumonitis. You can produce a pneumonitis in a human being by excessive dosage but why should we give it?

DR HENRY SCHMITZ, Chicago. Without entering into a discussion of the comparability of animal experimentation with our clinical observations on the human being, I have for years made the statement that when one massive treatment has been given—particularly for carcinoma—the treatment should not be repeated, because the tissue cannot stand a second full dose without permanent injury or damage. When we repeated a massive dose, within varying intervals, from six months to two years, we have regretted doing so. In each instance irreparable damage ensued from which the patient later succumbed. Let us content ourselves with one massive treatment as the surgeon is content with one operation. Recently we had an opportunity to observe a patient who was suffering from carcinoma of the breast. She had been treated elsewhere with interrupted frequent doses. We gave her a single massive treatment. After three years she developed a nodule which showed carcinoma. The treatment was repeated and before it was finished the patient became ill with an extreme disturbance of the heart, and it was six weeks before she finally recovered from the effects of this treatment.

DR E. A. POHLE. As far as measuring of the dose of roentgen rays in Dr Hartman's experiments is concerned, I will simply quote part of the resolution of the Standardization Committee of the Radiological Society of North America: "Voltage and filtration alone do not properly define radiation quality. It should be measured by a reliable ionization instrument." The same holds true for the quantity of radiation. As Dr Hartman stated, "No such instrument was employed" and this should settle the argument. I was interested in listening to Dr Pfahler's remarks. We agree as far as transferring the results of these animal experiments to human beings is concerned. In our first paper this fact was emphasized. Regarding the dose applied, there must have been a misunderstanding. We did not give three times a full dose within three months. The first time a full dose was given and the second and third time 50 per cent of it. In the old terminology it would amount to two erythema doses within twelve weeks. According to the so-called saturation method advocated by Dr Pfahler in 1925—such a procedure would be permissible in human therapy. He states that two full erythema doses of roentgen rays, of the penetration used in our experiments, may be given within from eight to twelve weeks. We must also consider that 600 R as adopted in our work as a tolerance dose (erythema dose) is identical with the surface dose because we used small fields. In therapy of conditions of the chest in people large fields of entry are employed adding about 40 per cent to the surface dose by back-scattering. Some laboratories use larger doses, up to 900 R measured in air, as erythema dose. A single exposure through a large field would bring the surface dose up to over 1,200 R. In our experiments this value is reached by the total dose given in divided doses over a period of three months. I do not feel, therefore, that this can be called excessive. The ratio of the irradiated volume to the total volume of the body is rather hard to establish. However, I would not be surprised if a comparison of the two ratios in human beings, using a 20 by 20 cm field of entry, and in rats treated over the heart with our technic will be in close proximity.

# THE HEART IN THYROID DISEASE

## I CHANGES IN THE T WAVE OF THE HUMAN ELECTROCARDIOGRAM FOLLOWING IODINE MEDICATION AND THYROIDECTOMY<sup>\*</sup>

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Fifty years before Graves' and Basedow's description of the symptom complex bearing their respective names, Parry and Flajani called attention to the occurrence of disturbances of the heart in association with goiter.<sup>1</sup> Adelman appears to have described two forms of disturbances of the heart in goiter, while Potain contributed a clinical discussion to the subject.<sup>2</sup> Rose first emphasized the importance of the heart in the sudden deaths of patients with goiter, believing that the effect on the heart was purely mechanical.<sup>2</sup> Schranz, however, and with him Wolfer and Wette, not entirely content with the mechanical theory, added reports of cases in which they believed nervous factors were also operative.<sup>2</sup>

In 1898, Friederich Kraus of Berlin described and differentiated various forms of goiter heart, dividing them finally into two principal groups, first, the mechanical goiter heart, and second, the monosymptomatic goiter heart.<sup>2</sup> The monosymptomatic goiter heart of Kraus was found in patients with goiter but without mechanical embarrassment of the circulation or respiration. Kraus believed that these cases never progressed to a true exophthalmic goiter but that they showed predominantly a cardiovascular syndrome, namely, increased cardiac activity, often tachycardia, a bounding, rapid pulse, in severe cases arrhythmia and in protracted grave cases, decompensation. Clinically and at autopsy the heart was enlarged to the left, in contrast to the mechanical form of goiter heart with enlargement of the right side.

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<sup>\*</sup> Submitted for publication, Aug 28, 1928

<sup>\*</sup> From the Thyroid Group Service and the Cardiographic Laboratory, Michael Reese Hospital

<sup>\*</sup> Read before a meeting of the Association of American Physicians, Atlantic City, May 3, 1927

1 Quoted from Klose. Die Basedowsche Krankheit, *Ergebn d inn Med u Kinderh* 10 182, 1913

2 Quoted from Chvostek, F. Morbus Basedowi und die Hyperthyreosen, Berlin, 1917, p 372



Chvostek<sup>3</sup> gave the most complete description of the heart in thyroid disease, classifying the various forms as follows

- 1 Mechanical goiter heart of Rose (the pneumatic or dyspneic goiter heart of Minnich)
- 2 The congestive goiter heart (substernal goiter) (goiter cardiaque, Revilliod)
- 3 Neurotic goiter heart (Wolfler) from pressure of the goiter on the vagus and sympathetic
- 4 Thyreotoxic goiter heart (Kraus)
- 5 Degenerative or torpid goiter heart (Bauer) (myxedema?)
- 6 Thyreopathic cardiac hypertrophy (Minnich) (myxedema?)

In a clinical discussion of the goiter heart, Gmelin<sup>4</sup> called attention to certain characteristics of the tachycardia, namely, that it is constant, even with rest in bed, and at night, that the tachycardia is not influenced by drugs or narcotics, and that it disappears promptly after operation. He spoke of the steep ascent and quick descent of the pulse wave during tachycardia which he believed is due to abnormal and persistent dilatation of small vessels. He described the heart beating violently against decreased peripheral resistance, the subjective sensation of warmth, the tendency to excessive perspiration and the profuse bleeding in the operative field during thyroidectomy, all evidence of the same capillary and arteriolar dilatation.

The present study is the first of a series of clinical and experimental observations concerning the heart in thyroid disease. While for many years this subject has been the recipient of much careful experiment and observation, there still appear to be many unsolved problems. Suggestive evidence of the desirability of further work concerning the rôle and integrity of the heart in thyroid disease may be seen from the following conflicting statements from both old and recent studies on this subject, some of them emanating from clinics where a vast amount of thyroid material is available for study.

Basedow patients suffer and die through their hearts (Moebsus)

Without tachycardia no Basedow (Charcot)

There are probably no cases of exophthalmic goiter in which cardiac symptoms are completely wanting (A Kocher<sup>5</sup>)

From a study of the data presented in this paper, the most outstanding fact is the infrequency in both exophthalmic goiter and adenoma with hyperthyroidism of symptoms indicating cardiac disease (Willius, Boothby and Wilson<sup>6</sup>)

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3 Chvostek, F. Morbus Basedowi und die Hyperthyreosen, Berlin, 1917, p 372

4 Gmelin, E. Zur Klinik des Kropfherzens, Arch f klin Chir **143** 726, 1926

5 Kocher, A., in Kraus and Brugsch. Spezielle Pathologie und Therapie, 1919, vol 1, p 751

6 Willius, F. A. Boothby, W. M. and Wilson, L. B. The Heart in Exophthalmic Goiter and Adenoma with Hyperthyroidism, M Clin N Amer **7** 189 (July) 1923

Young individuals with previously undamaged hearts suffer no cardiac changes, no matter how intense the thyroid toxicity (*Lahey and Hamilton*<sup>7</sup>)

It will be noted that in each of this series (hyperthyroidism) with one exception, the volume output of the heart per beat was diminished, it would therefore appear that all these patients had some heart failure (*Rabinowitch and Bazin*<sup>8</sup>)

With these conflicting opinions in mind, we propose to approach the problem from a number of separate points of view, both clinical and experimental, collecting data by methods in which the subjective element is eliminated or relegated, as far as possible, to the background

The widespread and enthusiastic reintroduction of iodine into the therapy of hyperthyroidism offers an additional reason for reopening the problem of the goiter heart. It is common experience that although in most cases and at certain stages in the evolution of exophthalmic goiter iodine has great value, in other cases and at other stages in the disease, it appears to be distinctly harmful. A number of interesting pieces of work are available in this connection. For example, in a study of the physiologic interrelations of the thyroid and heart, von Cyon<sup>9</sup> found that iodothyrim exerts a definite influence on the regulatory cardiac nerves, markedly increasing the normal excitability of the vagi and depressor nerves, and that it is effective in restoring the diminished excitability of these nerves as a result of thyroidectomy or degenerative disease of the thyroid gland.

Two years later, Barbera<sup>10</sup> confirmed von Cyon's observations, emphasizing as Boruttan had the antagonistic action of atropine and the stimulating effects on the vagi of iodine and iodothyrim.

Goodpasture<sup>11</sup> fed thyroid gland substance (thyroxin) to rabbits and produced areas of perivascular fibrosis and necrosis in the heart muscle. The same year, Hashimoto<sup>12</sup> produced experimental myocarditis in animals with toxic doses of dried thyroid substance and found interstitial tissue lesions not unlike the Aschoff-Tawara nodes in acute rheumatic fever.

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7 Lahey and Hamilton. Thyrocardiacs, Their Surgical Treatment, *Surg Gynec Obst* **39**:10 (July) 1924

8 Rabinowitch, I. M., and Bazin, E. V. The Output of the Heart Per Beat in Hyperthyroidism, *Arch Int Med* **38**:566 (Nov) 1926

9 Von Cyon. Zur Physiologie der Schilddrüse und des Herzens, *Pflügers Arch f d ges Physiol* **70**:511, 1898

10 Barbera. Einfluss von Iodin, Iodonatrium und Iodothyrim auf der Kreislaufs, *Pflügers Arch f d ges Physiol* **79**:312, 1911

11 Goodpasture, E. W. The Influence of Thyroid Products on the Production of Myocardial Necrosis, *J Exper Med* **34**:407, 1921

12 Hashimoto, H. The Heart in Experimental Hyperthyroidism with Special Reference to Its Histology, *Endocrinology* **5**:579, 1921

In an interesting study of metabolism of iodine, with particular reference to the level of iodine in the blood under various conditions, Veil and Sturm<sup>13</sup> found an increase of iodine (hyperiodemia) during tachycardia, and sympathetic stimulation by epinephrine and a decrease (hypo-iodemia) in vagus stimulation with pilocarpine and under digitalis medication

Takane<sup>14</sup> believed that acute myocarditis, produced experimentally by inorganic iodine compounds, was caused by the liberation of free iodine and by the large amounts of lactic acid present in the actively contracting heart muscle

A summary of these studies shows that

Iodothyrim increases the excitability of the vagus and depressor nerves

Thyroxin produces perivascular and interstitial fibrosis and necrosis of the heart muscle

Sympathetic stimulation causes hyperiodemia

Vagus stimulation causes hypo-iodemia

Experimental iodine myocarditis develops because of the excessive amounts of lactic acid in heart muscle unbound by protein, uniting with inorganic salts and liberating free iodine

In other words, one may conclude from these and similar studies that under certain conditions iodine exerts a positive (harmful?) effect on both the regulatory cardiac nerves and the cardiac musculature

Bearing in mind these conflicting views concerning the frequency of the involvement of the heart in thyroid disease and of the effects of iodine and of thyroid substance on heart muscle and cardiac nerves, we decided first to direct our attention to the electrocardiographic examination in persons with thyroid disease. In this paper we will present the results of an electrocardiographic study of patients suffering with varying degrees of thyrotoxicosis, the condition at the height of the disease before treatment, the changes in the electrocardiogram occurring during iodine medication, and the condition following operation

Hoffman<sup>15</sup> appears to have been the first to describe the high T wave in the electrocardiogram of patients suffering with exophthalmic goiter. In twenty-three patients with the so-called thyrotoxic heart, a high T wave was found in lead II, the height of the wave being proportional to some extent to the rapidity of the heart beat. Almost a decade later,

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13 Veil, W. H., and Sturm, A. Iodin Metabolism, *Deutsches Arch f klin Med* **147** 166, 1925

14 Takane, K. Pathobiogenese der Myocarditis acuta durch organische und anorganische Jodbindungen bzw der Basedomoyokarditis, *Virchows Arch f path Anat* **259** 11, 1926

15 Hoffman, A. Die Elektrokardiographie, Wiesbaden, 1914, p 108

Krumbhaar,<sup>16</sup> apparently unacquainted with Hoffman's work, described "unusually prominent T wave in most cases of toxic goiter, which in about half the cases were markedly and persistently diminished after operation" In a large series (377 patients) of electrocardiographic observations of the heart in exophthalmic goiter and adenoma with hyperthyroidism, Willius, Boothby and Wilson<sup>17</sup> refrained from commenting on the height of the T wave, except to call attention to the infrequency (1 per cent) of inversion of the T wave

Confirmatory, though indirect, evidence of the significance of the height of the T wave in persons with hyperthyroidism is available in a number of studies of the heart in hypothyroidism In persons with myxedema, Zondek<sup>18</sup> found both the P and the T waves practically absent, with a gradual return of the waves following thyroid medication From observations in four cases, Fahr<sup>19</sup> believed that inversion of the T wave in lead I was characteristic of the heart in myxedema, though later it became upright under thyroid medication From a study of a large series (168) of cases of myxedema, Willius and Haines<sup>20</sup> concluded that "actual myxedematous change in the myocardium explains the electrocardiographic abnormalities that disappear with treatment" The abnormalities referred to are inversion of the T wave in various leads

#### PLAN OF WORK

As soon as possible after admission to the thyroid group service, patients were placed at complete rest in bed, and control readings of the basal metabolism, electrocardiograms, blood pressure determinations and distance roentgenographic examinations of the heart were made Following the completion of this control data, compound solution of iodine (Lugol's solution) was started, 10 minims being given three times daily after meals, the foregoing examinations being repeated at frequent and stated intervals during the course of iodine medication After varying periods of from two to three weeks, sometimes longer, patients were submitted to subtotal thyroidectomy under ethylene anesthesia At certain intervals following operation, the foregoing data were again obtained Thirty-two cases have been studied, and the data from them

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16 Krumbhaar, E B    Electrocardiographic Observations in Toxic Goiter, *Am J M Sc* **155** 175, 1918

17 Willius, F A, Boothby, W M, and Wilson, L B    Heart in Exophthalmic Goiter and Adenoma with Hyperthyroidism, *M Clin N Amer* **7** 189 (July) 1923

18 Zondek, A    Herzbefunde bei endokriner Erkrankungen, *Deutsche med Wchnschr* **46** 1239, 1920

19 Fahr, G E    Myxedema Heart, *J A M A* **84** 345 (Jan 31) 1925

20 Willius, F A, and Haines, S F    Status of the Heart in Myxedema, *Am Heart J* **1** 67, 1925

will be presented in collective form. Electrocardiograms and drawings enlarged to scale illustrating the most significant observations are appended.

#### RESULT

Tachycardia was present before treatment in practically all cases, the pulse rate being roughly proportional to the severity of the thyrotoxicosis and the level of the basal metabolism. The T wave was increased in height in several cases, but the increase was not uniform and apparently

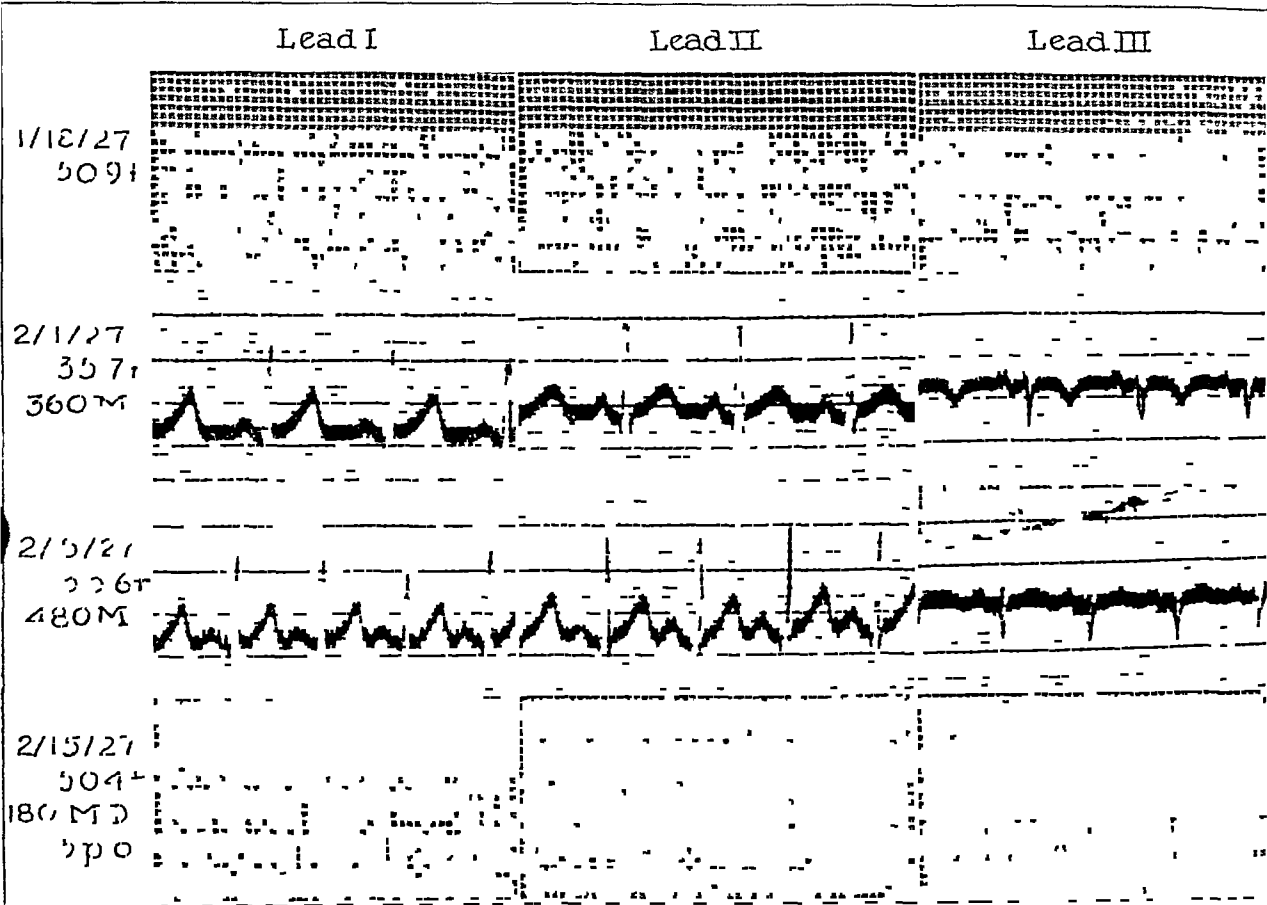


Fig 1 (case 3) —Mildred R, a schoolgirl, aged 15 years, simple (adolescent?) goiter for past year, with sudden severe exacerbation two weeks before admission (acute exophthalmic goiter) during iodine medication. Increase of  $T_2$  during administration of iodine with signs of decompensation. Slight improvement with digitalis. Death immediately following thyroidectomy. Pathologic examination showed hyperplasia of the thyroid with colloid invasion, focal areas of hyperplasia and moderate fibrosis.

had little if any relation to the pulse rate. Preliminary rest in bed without iodine resulted in a slight decrease in the pulse and basal metabolic rates, but was without effect on the height of the T wave. In most cases, iodine caused a varying degree of depression of the basal metabolic and

the pulse rates and in the majority of instances, a lowering of the T wave. There were, however, many exceptions to the latter, several cases not showing an apparent change. One showed a slight increase in height and one a marked increase with increase in the pulse rate and signs of decompensation. In some cases, changes in the T wave were the only ones observed, others showed a proportional decrease in the height of the P wave and still others, a decrease in the height of all waves.

The effects of thyroidectomy were more uniform. The T wave became definitely lower in most instances following operation, the degree of lowering being roughly proportional to the level of the basal metabolic and pulse rates, irrespective of the height of the wave prior to operation and iodine medication. This postoperative depression remained permanent in most instances, as long as the patient remained under observation, although two cases finally showed a gradual return to

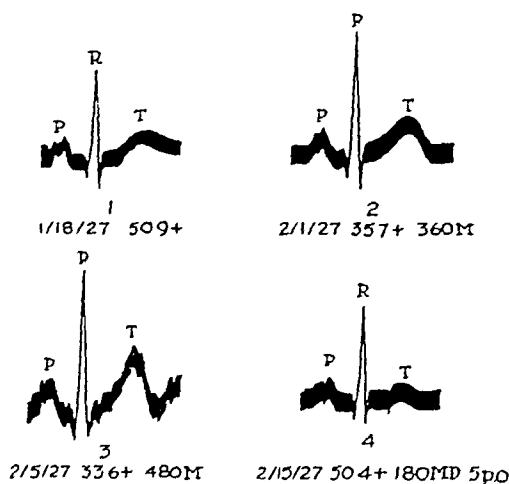


Fig 2—Enlarged drawing (to scale) of electrocardiographic complexes (lead II, fig 1), showing changes in T wave during iodine medication and following thyroidectomy (4). Enlarged drawing showing (a) the date curve was made, (b) basal metabolic rate, (c) amounts of compound solution of iodine (Lugol's solution) administered up to that time expressed in minims.

the preoperative level. In two cases, the lowering of the wave progressed to a definite inversion, the basal metabolic rate meanwhile not showing a proportional decrease. The degree of inversion of the T wave varied at definite periods following operation with, however, a gradual return to a point just below the preoperative level.

In the two cases showing inversion of the T wave, the negativity occurred after a rather long iso-electric period from the foot of the R wave, what might be called delayed inversion. This type of inversion is in contrast to the immediate inversion of the T wave from digitalis, and the "cove"-shaped T wave of coronary occlusion.

While in most cases the changes in the T wave were most striking, several cases showed parallel changes in the other waves. In practically

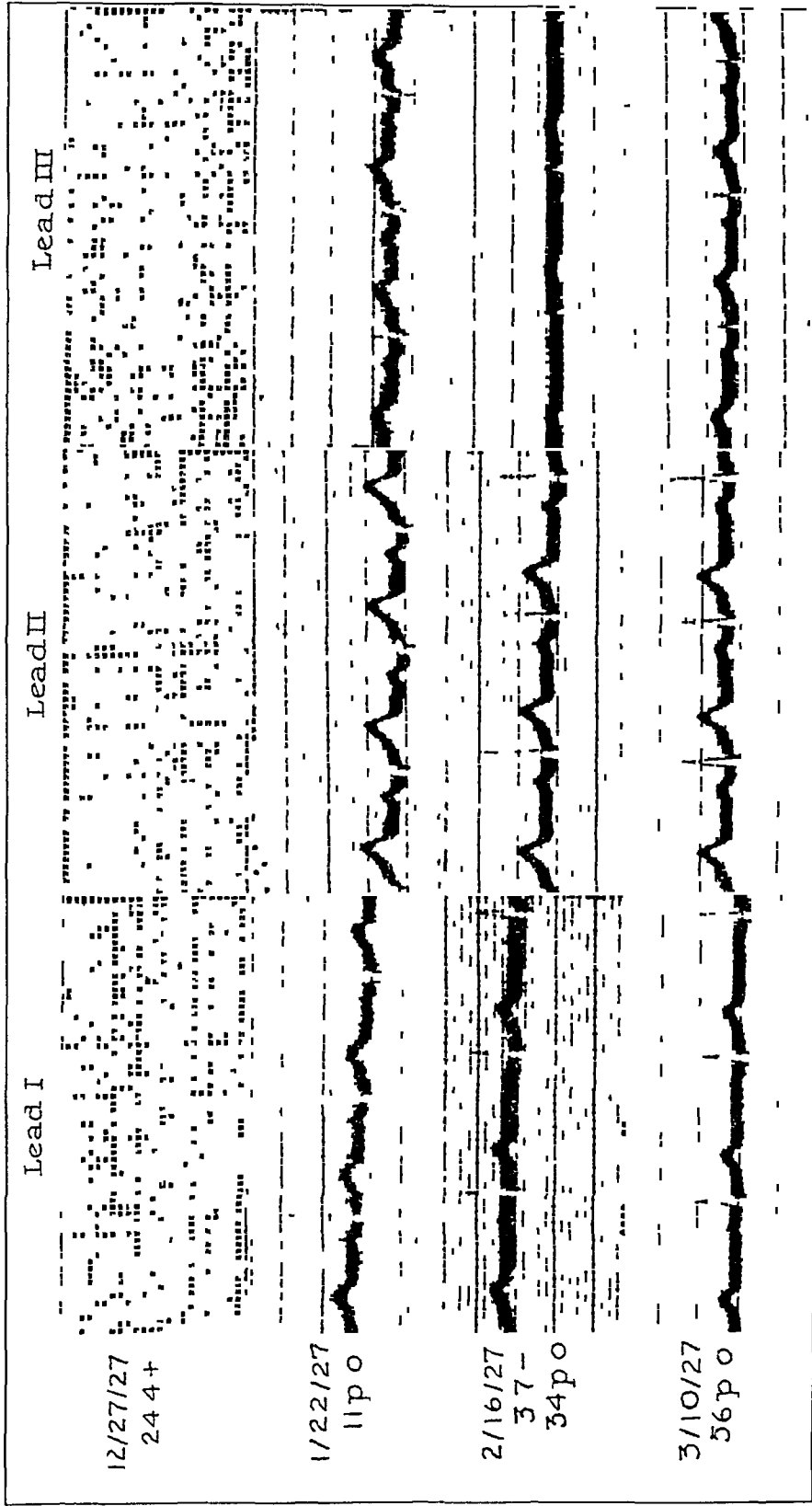


Fig 3 (case 4) —Miss Bertha S, a school teacher, aged 47 Toxic adenoma of eight years' duration, with severe acute exacerbation of symptoms (sympathetic nervous system) for the past three to four months Unusually high T waves occurred in all leads during administration of small amounts of iodine, with marked decrease eleven days after thyroidectomy, with still further lowering of T, thirty-four days after operation

all instances, as the T wave decreased in height the R-T interval lengthened, and conversely

In searching for an explanation of the source of these observed electrocardiographic changes, one must consider certain facts and characteristics concerning the T wave. Without attempting to discuss at length the various theories and beliefs concerning the nature of the T wave, both experimentally and clinically, all that we wish to call attention to is the generally accepted fact of the extreme lability of the T wave, a phenomenon observed and commented on by all workers in this field <sup>21</sup>

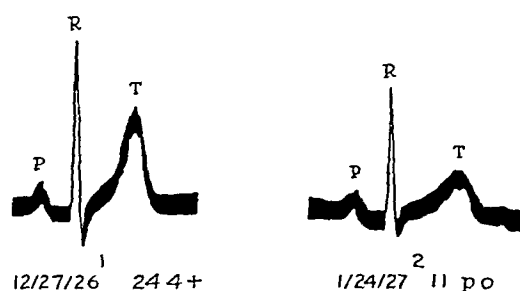


Fig 4—Enlarged drawing (to scale) of electrocardiographic complexes (lead II, fig 3), showing high peaked  $T_2$  and a basal metabolic rate of  $244+$  before treatment, with decrease in height of  $T_2$  occurring eleven days postoperatively (subtotal thyroidectomy)

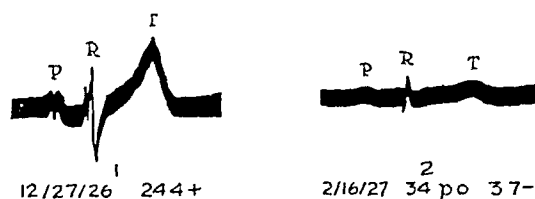


Fig 5—Enlarged drawing (to scale) of electrocardiographic complexes (lead III, fig 3), showing high peaked  $T_3$  before treatment with marked lowering (almost to iso-electric line) of  $T_3$ , thirty-four days postoperatively, with a basal metabolic rate of 37 per cent minus

To quote from Lewis <sup>22</sup>

It is agreed by most workers that in its direction and form, T is much less stable than are the initial (ventricular) deflections. Thus vagal or sympathetic stimulation may exert a profound influence on the end deflection though the initial deflections are affected slightly. Many poisons act similarly. As Cohn and his

21 Katz and Weinman. The Relation of the T Wave to the Asynchronism Between the Ends of Right and Left Ventricular Ejection, *Am J Physiol* **81** 360, 1927, found "no consistent relation between changes in the T wave and variations in synchronism of the end of right and left ejection"

22 Lewis, T. The Mechanism and Graphic Registration of the Heart Beat, ed 3, London, Shaw & Sons, 1925, p 120



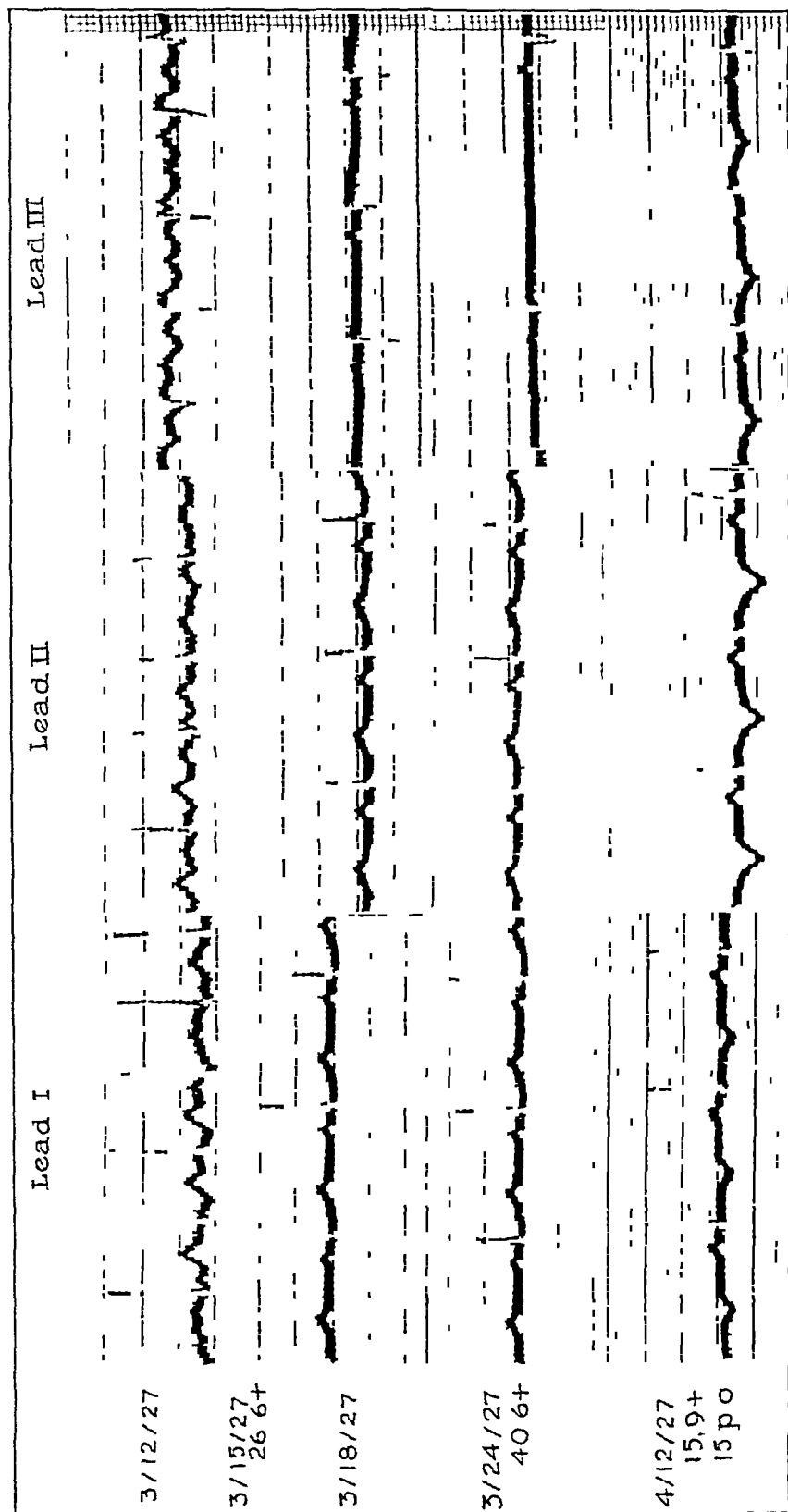


Fig 6 (case 6)—Mrs Ann J, housewife, aged 62 Toxic symptoms of one year's duration following influenza, with attacks of paroxysmal fibrillation and sino-auricular block T waves low throughout — iso-electric in lead III No change after iodine, quinine or digitalis medication Inversion of the T wave occurred in all leads, following thyroidectomy

co-workers<sup>23</sup> have shown, an early effect of digitalis intoxication in man is to invert T deflection, QRS remaining unchanged

The reference to vagal and sympathetic stimulation emanates largely from the experimental observations of Rothberger and Winterberg. The accompanying table (taken from Tigerstedt<sup>24</sup>) summarizes their most important conclusions

*Summary of Conclusions of Rothberger and Winterberg*

Condition of Regulatory Nerves	P	R	T
High vagal tone	low	high	low
Vagal activity (right ventricle)		high	low
Fall in accelerator tone (Stellectomy)	low	high	low
High accelerator tone	high	low	high
Stimulation right accelerator	high	low	diphasic
Stimulation left accelerator	low	(deep S)	inverted

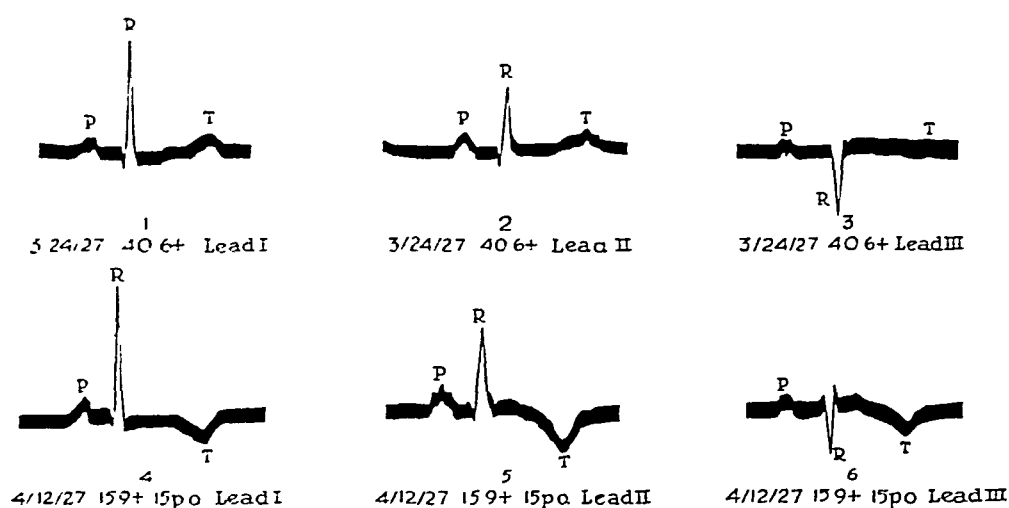


Fig 7—Enlarged drawing (to scale) of electrocardiographic complexes, all leads (fig 6), showing inversion of T wave in all leads, fifteen days postoperatively (thyroidectomy)

On the basis of these results it is suggestive that the observations described, resulting from iodine medication and following thyroidectomy, are due, at least in part, to variations in vagal and sympathetic (accelerator) tone. These variations in tone are probably due, in the first instance, to the effects (hypertonicity?) of the thyrotoxicosis on the regulatory nerves, the later changes, to the modifying influence of iodine and thyroidectomy. These results bring additional evidence to support the view, long held, that increase and variation in sympathetic and vagal

23 Cohn, Fraser and Jamieson. Influence of Digitalis on the T Wave of the Human Electrocardiogram, *J Exper Med* **21** 593, 1915

24 Tigerstedt. *Die Physiologie des Kreislaufs*, Berlin and Leipzig, Walter De Gruyter & Co., 1923, vol 2, p 400

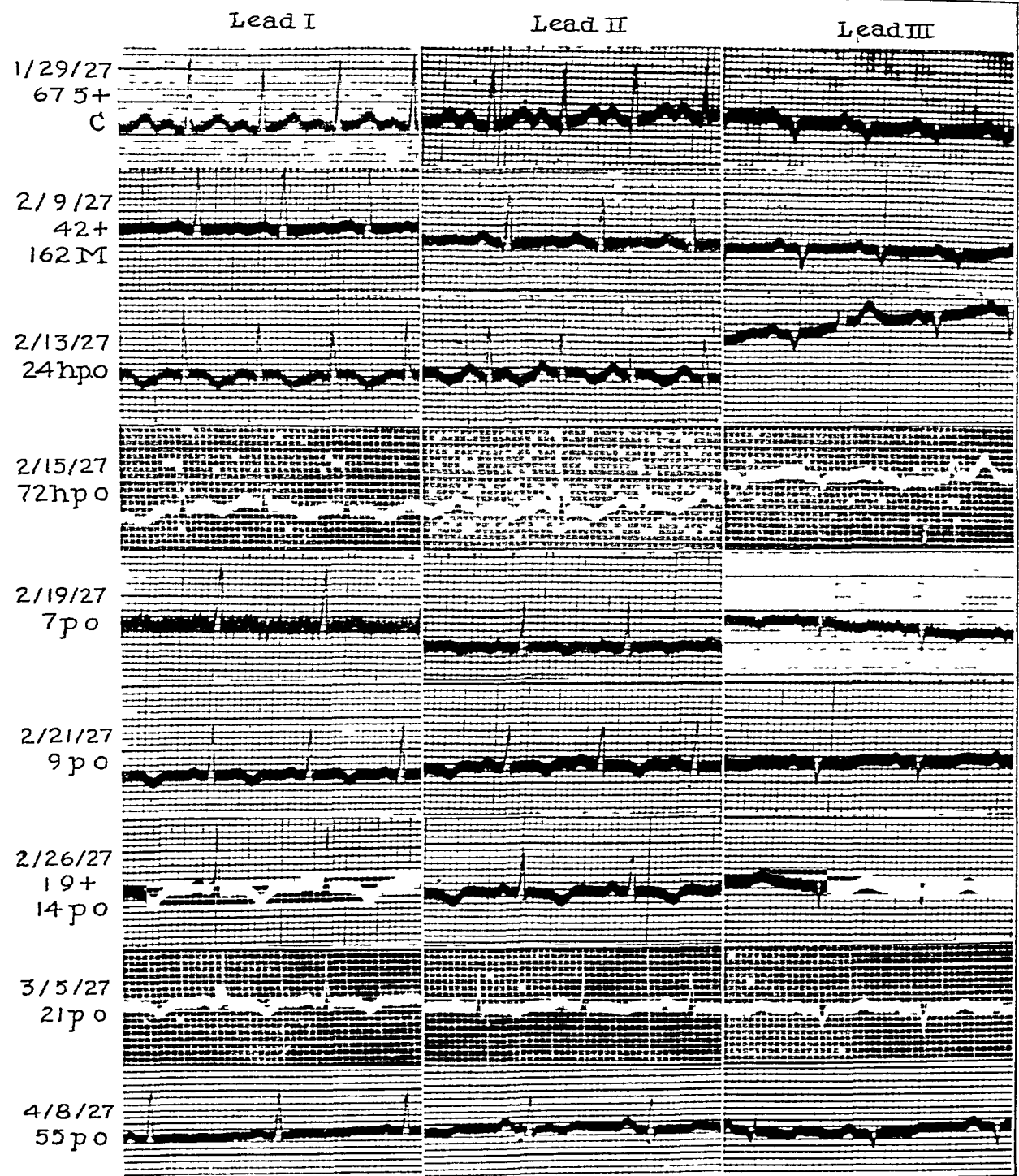


Fig 8 (case 8)—Mrs E O A, aged 38, a housewife Toxic adenoma with sudden onset one year before presentation Normal T waves at onset, with marked lowering during administration of compound solution of iodine (Lugol's solution), progressing to inversion immediately following thyroidectomy, inversion continuing for three weeks postoperatively, with varying degrees of negativity, becoming iso-electric and diphasic eight weeks following operation

tone are features in the symptom complex of hyperthyroidism and probably explain the electrocardiographic changes seen during the course of medical and surgical treatment

These results do not permit any definite conclusions to be drawn as to the effects of thyrotoxicosis on heart muscle, and while we feel that such is undoubtedly the case, objective evidence supporting this view must be sought from other sources. Whether iodine can produce similar

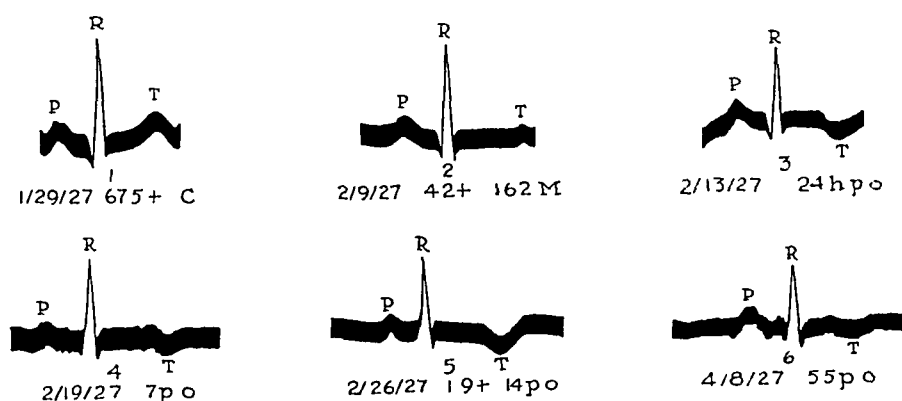


Fig 9—Enlarged drawing (to scale) of electrocardiographic complexes (lead II, fig 8), showing marked lowering of T wave following administration of 162 minims of compound solution of iodine (Lugol's solution), with inversion of T wave postoperatively

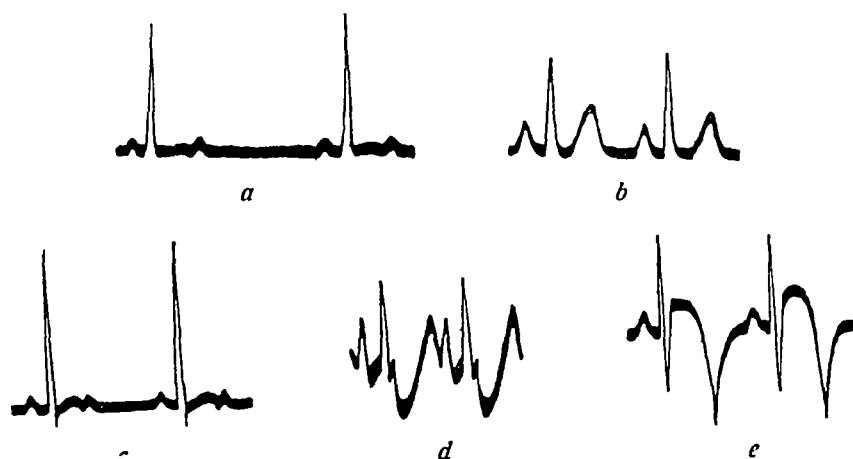


Fig 10—Taken from Tigerstedt (*Die Physiologie des Kreislaufes*, Berlin and Leipzig, Walter De Gruyter & Co, 1923, vol 2, p 400), showing changes in the electrocardiogram resulting from nerve stimulation: *a*, normal high vagal tone, *b*, normal good accelerator tone, *c*, effect of absence of accelerator tone, *d*, stimulation of right stellate ganglion and *e*, stimulation of left stellate ganglion

cardiac changes in normal persons cannot be definitely answered at this time. In two control patients included in this series, the results are conflicting, one showing similar changes in the T wave, one not showing any changes (fig 11). We plan a larger series of control cases in the near future.

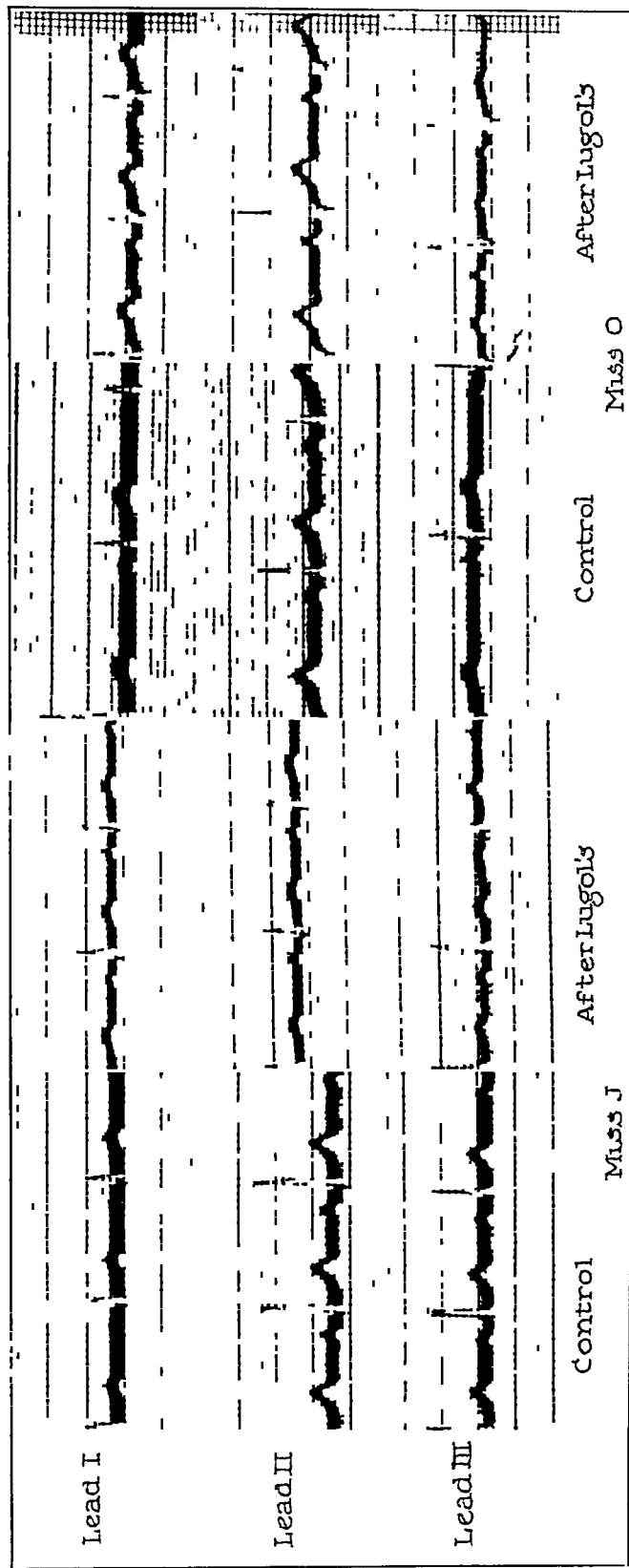


Fig 11—Administration of compound solution of iodine (Lugol's solution) caused slight decrease in the T wave in all leads of the first normal person (Miss J), but no change in the second (Miss O). The basal metabolic rate remained stationary in both

Our observations likewise raise the question whether some part of the favorable influence of iodine medication in persons with hyperthyroidism may not be due to direct effects on the sympathetic and vagus system, independent of its effect on the thyroid, or possibly on these nerve structures through and by way of the thyroid or possibly both.

While, as we have stated, these results do not permit the drawing of definite conclusions regarding the heart muscle, it is of course obvious that a possible factor in the explanation of these electrocardiographic changes is the effect of toxic thyroid substance and iodine on heart muscle. In order to reach a definite decision regarding this, we are having recourse to direct experiment on animals as well as further work in the clinic concerning the use of barium chloride and atropine, which will be reported later.

The likelihood that diminution and inversion of the T wave may be caused, at least to some extent, by the effects of iodine on heart muscle appears likely from the effects of other drugs on the T wave, notably digitalis. If this is so, it would mean that iodine and iodothyrim may cause alterations in the muscular state of the heart. The preponderance of electrical activity persisting longer in the region of the apex than at the base, that is to say, the greater electric activity near the apex, would account for apex negativity and consequent inversion of the T wave.

#### CONCLUSIONS

- 1 Iodine medication (compound solution of iodine [Lugol's solution]) in hyperthyroidism results in most instances in diminution of the height of the T wave of the human electrocardiogram.
- 2 The remaining cases did not show any change in the T wave. A few showed an increase in the height of the T wave. In one of the latter, symptoms of decompensation developed coincidentally.
- 3 Subtotal thyroidectomy is followed by an even greater lowering of the T wave, in two cases progressing to inversion.
- 4 Decrease in the basal metabolic rate proceeds parallel to a decrease in the height of the T wave following iodine medication and thyroidectomy.
- 5 The variations in the height and form of the T wave described are probably to be explained both by variations in tone of the regulatory cardiac nerves (vagus and sympathetic) as well as by alterations in the muscular state of the heart.
- 6 Inversion of the T wave following thyroidectomy appears as a delayed inversion, in contrast to the immediate inversion occurring after the administration of digitalis and the cove-shaped inversion of coronary occlusion.

# SPECIFIC SERUM TREATMENT IN CHRONIC ULCERATIVE COLITIS\*

J ARNOLD BARGEN, M D  
ROCHESTER, MINN

Vaccine prepared from the diplostreptococcus, which I isolated in 1924<sup>1</sup> and which appears to have etiologic significance, has been shown to be of value in the treatment of patients with chronic ulcerative colitis. Various reports have appeared in the literature on the results of treatment in isolated cases, and the treatment has been used in a considerable number of unselected cases in the Mayo Clinic. The treatment has been most successful in cases of chronic invalidism in which the temperature is normal or nearly normal, the secondary anemia is only moderate and the disease has run a progressive downward course, yet apparently leaving in the patient a fighting reserve. The vaccine apparently has little value in the small group of cases in which symptoms of the disease develop rapidly as an acute fulminating illness, with fever, leukocytosis, abdominal cramps, tenesmus, many bloody, purulent rectal evacuations and rapid wasting. In these cases the patient's protective forces are taxed to the utmost by the infection, and further call on the mechanism of antibody formation goes unanswered.

The first attack of acute ulcerative colitis or acute exacerbation of chronic ulcerative colitis is striking and characteristic. The patient is acutely ill, the fever is septic, the abdomen is diffusely tender, there may be cold perspiration, the facies is frequently anxious and severe cramps may accompany the frequent rectal discharges. Often the patient complains bitterly of soreness and tenderness of the anus. The proctoscopic picture is pathognomonic, and an experienced proctologist does not confuse it with that of any other rectal disease. This is the stage of intense edema and hyperemia with myriads of miliary abscesses studding the mucosa, some of which have broken down to form minute ulcers. By carefully cleansing and, as nearly as possible, sterilizing the rectal mucosa through an anoscope, the tip of a minute Pasteur pipet may be inserted into any of the minute abscesses and a tiny drop of pus withdrawn which contains the diplostreptococcus of chronic ulcerative colitis<sup>2</sup> (fig 1)

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\* From the Division of Medicine, The Mayo Clinic

1 Bargaen, J A. Experimental Studies on the Etiology of Chronic Ulcerative Colitis. Preliminary Report, J A M A 83 332 (Aug 2) 1924

2 Bargaen J A. The Medical Management of Chronic Ulcerative Colitis, A Statistical Study of 200 Cases, Tr Am Gastro-Enterol A, 1927, p 145

Roentgenograms by barium enema also present characteristic signs. Intense spasm permits barium to enter the colon only with difficulty and causes its rapid expulsion (fig 2).

Passive immunization of a patient with such a fulminating infection against the causative organism seems rational. With this idea in mind and for the purpose of producing a serum of diagnostic value, an effort was made to secure an immune serum in horses. Rosenow prepared the serum by injecting two horses with increasing doses of freshly isolated strains of the diplostreptococcus and by using several of these after preservation in dense suspensions in a mixture of two parts of glycerine



Fig 1—The diplostreptococcus of chronic ulcerative colitis,  $\times 1,000$

and one part of saturated sodium chloride solution during the period of immunization (fourteen and nine months, respectively). This method has been shown to preserve specificity of streptococci for a long time, and for this reason Rosenow has used it in the preparation of poliomyelitis, encephalitis and other antistreptococcus serums. The serum was not used for treatment until after immunization had been continued for five months, and until it had a high agglutinating and precipitating titer, as well as protective power against the experimental disease in rabbits.<sup>3</sup> Intravenous injections were given on three successive days each week, beginning with twenty-five billion dead organisms. The dosage was

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3 Results along these lines to be published elsewhere



gradually increased to two thousand billion organisms. After immunization had been continued for two and four months, respectively, live organisms were given. Bleedings were made from seven to ten days after the last previous injection, at intervals of from three to six weeks,

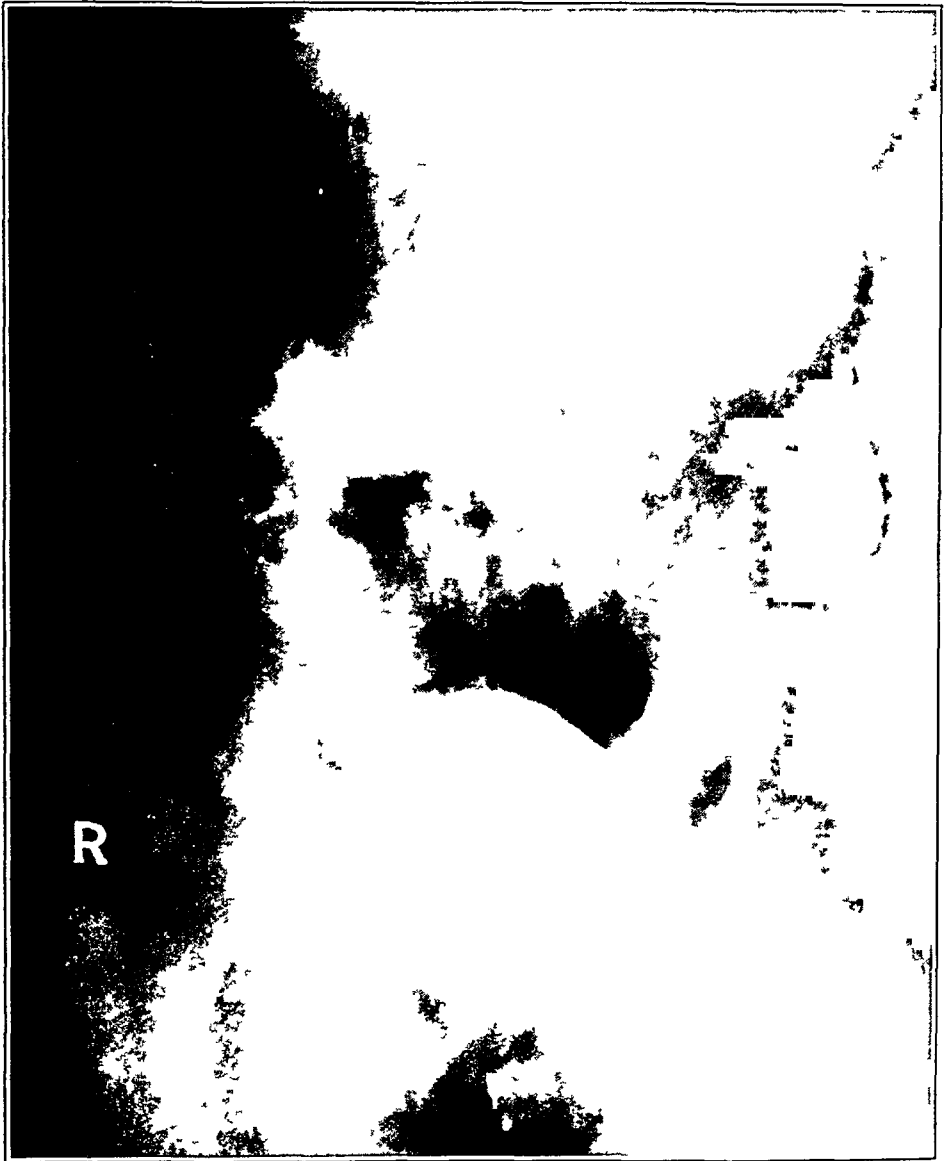


Fig 2—Typical roentgenogram by barium enema in a case of acute ulcerative colitis of the chronic ulcerative colitis type

depending on the condition of the animal. The bleedings were made in a sterile manner from the jugular vein. The serum was drawn from the clotted blood after squeezing the clot with tinned weights for from twenty-four to forty-eight hours. Two-tenths per cent cresol was added as a preservative. It was proved sterile by making aerobic partial

tension and anaerobic cultures<sup>4</sup> and proved nontoxic by intravenous injection into guinea-pigs

In eleven cases, deep muscular injections of the serum were given in repeated daily increasing doses over a period of from three to six days. In eight, what was considered an adequate amount was given. Four subjects were not suitable for treatment by serum, the condition in these cases was chronic, and the patients had not responded to other means of treatment. In the seven acute cases in which adequate amounts of serum were given, two patients were clinically well and have been so for seven and twelve months, respectively. The other five patients were permanently improved, the fever subsided, the blood in the stool decreased or stopped and movements were reduced to a minimum, but none was entirely relieved from symptoms. Three patients were able to carry on their business. Two patients died, one of these was improved by the serum but died at his home several months later from advancing chronic disease, the other died after ileosigmoidostomy for a suspected malignant condition, the disease had spread to the ileum and terminated finally in multiple perforations and peritonitis.

It should be noted that the condition in all seven cases was an acute fulminating ulcerative colitis. A few years ago ileostomy was performed in such cases with a high mortality rate as the result. In at least six of the seven cases, ileostomy was not necessary because the serum was used. In the present state of knowledge ileostomy must still be performed in certain cases, but it is not always easy to decide the proper time for performing it. If the patients survive the operation, the ileostomy may be permanent. Since the use of vaccine prepared from the diplococcus of chronic ulcerative colitis and the use of the specific immune serum, ileostomy has become limited to a few advanced cases in which reserve apparently has been so depleted and in which there is so much destruction of tissue that antibodies cannot develop apace with infection, and to cases with such complications as malignant growth, stricture and perforation.

Early diagnosis of chronic ulcerative colitis is imperative. A careful proctoscopic examination should be made by a competent proctologist in all cases of diarrhea. Removal of foci of infection and the administration of vaccine or serum in the proper cases promises a control of this dreaded disease.

#### REPORT OF CASES

CASE 1—A man, aged 52, a dealer in coal and ice, came to the Mayo Clinic on Nov 15, 1926, with a history of bloody diarrhea (discharges about every hour) with general abdominal cramping of six weeks' duration. The leukocytes num-

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<sup>4</sup> Rosenow, E. C. Studies on Elective Localization of Focal Infection, with Special Reference to Oral Sepsis, *J. Dent. Research* 1: 205, 1919.

bered 26,000. He had lost 40 pounds (18.1 Kg) in weight in six weeks. The temperature was from 99.5 to 100 F. The Wassermann reaction of the blood was negative. Gastric acids were 60 and 48. The urine was normal. Sputum and smears from the rectal discharge did not disclose acid-fast bacilli. Parasites or ova were not found in the stool. The tonsils were infected, and one tooth contained periapical abscess. The proctoscopic picture was that of rather active chronic ulcerative colitis, the rectal mucosa was studded with innumerable small ulcers, and the mucosa bled easily. Roentgenograms of the colon were negative.

The patient was given injections of filtrate prepared from the diplococcus of chronic ulcerative colitis in increasing doses every third or fourth day. He also received tincture of iodine, 10 drops to a dose, for a few days. He was dismissed on December 10, when one or two formed stools were being passed daily. He was instructed to continue the treatment by filtrate at home and to have his tonsils removed. On February 5, he reported by letter that he had a slight exacerbation of trouble, this grew worse gradually, and he returned to the clinic on February 12. About thirty bloody, purulent stools were being passed every twenty-four hours.

On February 14, the proctoscopic picture was that of acute severe exacerbation of the disease. From February 15 to 19 inclusive, 15, 20, 30, 33 and 50 cc of concentrated immune serum of chronic ulcerative colitis was given. On February 21, following a three-day gradual decrease in stools, one formed stool was passed. The proctoscope on February 22 showed the mucosa of the sigmoid to be normal and that of the rectum greatly improved. The patient was dismissed from observation on February 26 clinically well, and was given an autogenous filtrate to take at home. He remained well and returned for tonsillectomy on April 22. An eighteen hour culture of the macerated tonsils was injected into two rabbits, one rabbit in which lesions were not demonstrable elsewhere in the body, died in forty-eight hours from acute ulcerative colitis, the other rabbit suffered from diarrhea but recovered. The proctoscopic examination on April 28 showed the mucosa of the bowel to be entirely normal with only a tendency to bleed on trauma. From February 22 to April 22, the patient gained 22 pounds (10 Kg). He was instructed to continue treatment by filtrate for several months.

In a letter written on October 10, the patient stated that he was still well. The serum reaction came three weeks after the first injection of serum as severe urticaria. Except for one slight upset, which lasted two weeks, and which was promptly controlled by vaccine, this patient has not had any diseased condition of the bowels for a year.

CASE 2—A woman, aged 27, a farmer's wife, came to the Mayo Clinic on March 15, 1927, complaining of bloody diarrhea of five months' duration. This condition had started with ten to twelve soft bowel movements daily, the stools containing mucus, pus and blood. On admission she felt weak and had a poor appetite. The temperature was 99 F at 2.30 p.m. The tonsils were infected but the results of the examination otherwise were negative. The hemoglobin content was 65 per cent. the Wassermann reaction of the blood and tests of the urine were negative. In three stools examined on three successive mornings, parasites or ova were not found. Roentgenograms showed that the teeth were normal. A roentgenogram of the colon showed that the disease involved the colon to the splenic flexure. The proctoscopic picture showed marked diffuse hyperemia and edema, with innumerable minute ulcers, graded 2. At this time the patient was passing from twelve to fifteen rectal discharges daily.

The patient was hospitalized and given five deep muscular injections of the concentrated immune serum of chronic ulcerative colitis, that is, 15, 20, 30, 40 and 50 cc over a period of five days. She had serum sickness with marked urticaria.

and pains in the joints, beginning three days after the last injection, which lasted five days. Three days after the last injection of serum, the rectal discharges averaged two daily, there was no trace of blood. She was dismissed and urged to have her tonsils removed after three weeks. She was free from symptoms until June 1, at which time mild symptoms gradually returned. The tonsils had not been removed. An autogenous vaccine prepared from the diplococcus isolated from the ulcers in the rectum was given. After fifteen injections the symptoms subsided. The vaccine was continued and on September 27, the patient again reported that she was free from symptoms. The tonsils have not been removed. There has not been a recurrence for seven months, and the patient is clinically well.

CASE 3—A man, aged 23, came to the Mayo Clinic on Dec. 29, 1926, complaining of bloody, purulent diarrhea of seven months' duration. He was brought on a stretcher and was extremely emaciated. He had lost 35 pounds (15.9 Kg.) within six months. There were from ten to fifteen daily rectal discharges—he also suffered from acute polyarthritis.

Examination revealed the patient to be extremely ill, weak and anemic, with severe perianal ulceration. The hemoglobin was 50 per cent. Results of urinalysis were negative. Gastric analysis showed total acid 24 and free acid 10. A culture of the blood was negative on Jan. 3 and 11, 1927. Roentgenograms showed the teeth, chest, kidneys, ureters and bladder to be normal. There was a small tonsillar tag. A roentgenogram of the colon showed a lesion of the entire descending colon suggestive of polyposis. Results of examination of eight successive stools on as many mornings were negative for parasites and ova. Culture of the rectal ulcers revealed nearly a pure culture of diplococci of the morphology of those found in chronic ulcerative colitis. The proctoscope above the extensive anal ulceration showed normal mucosa up to the lower part of the sigmoid, where the picture was that of acute ulcerative colitis. Prostatitis graded 4 was present.

For several months attempts were made to clear up the perianal ulceration with local applications and various systemic medications, including cod liver oil, Blaud's pills, tincture of iodine, morphine, bismuth, gentian violet and an autogenous vaccine, when these failed, the patient was given deep muscular injections of 15, 20, 20, 20 and 30 cc. of the immune serum of chronic ulcerative colitis from April 7 to 11, inclusive. From December until April, the temperature ranged from 99 F to 102 F daily. The immediate reaction from the serum was the slight daily elevation of temperature, from 102 to 103 F. Three days after the last injection of serum was given, the temperature receded to a maximum of 99 F and was usually normal for four days. On April 17, the temperature went to a maximum of 101 F and reached this point almost daily for several weeks. There was gradual improvement, and the patient was finally dismissed on May 2, in fairly good health.

Sickness from the serum, as marked urticaria, began two days after the last injection of serum was given, and lasted for four days. The patient was given a filtrate to be administered subcutaneously at home. He returned August 5, definitely improved and weighing 136 pounds (61.7 Kg.), a gain of 9 pounds (4.1 Kg.) since his dismissal. During the months he was at home he was up and about daily. He returned on October 4, with a history of marked general improvement but severe abdominal cramps in the upper part of the abdomen preceding each bowel movement, of which he averaged two in twenty-four hours. The average during the severe illness was from ten to fifteen. A roentgenogram of the colon at this time showed a filling defect at the hepatic flexure, which was thought to be malignant.

Exploration was carried out on October 13. An ileosigmoidostomy was made, with the idea of performing hemicolectomy later. The surgeon believed that the

growth was malignant. Grossly, there was the typical picture of healing following chronic ulcerative colitis of the descending colon, which was narrowed and fibrous. Following ileosigmoidostomy, symptoms of colitis recurred. The patient died five weeks later of multiple perforations of the small intestine, the colitis having extended since the ileosigmoidostomy up the ileum to involve about half of the ileum and parts of the jejunum. There were several small acute ulcers in the stomach.

CASE 4—The patient was a woman, aged 25, whose trouble had begun insidiously one year previously. During the first six months, defecation took the form of a discharge of bloody, purulent material, the number of stools averaged six daily. Then the number increased to an average of fourteen, with more bright red blood and mucus and pus. That number had not increased by the time of admission. The patient had lost 48 pounds (21.8 Kg) in weight during the two years.

On admission, Aug. 24, 1927, the patient complained of cramps in the lower part of the abdomen and a griping pain before defecation. The temperature was 99.6 F, and the pulse rate 120. A roentgenogram showed a periapical abscess.

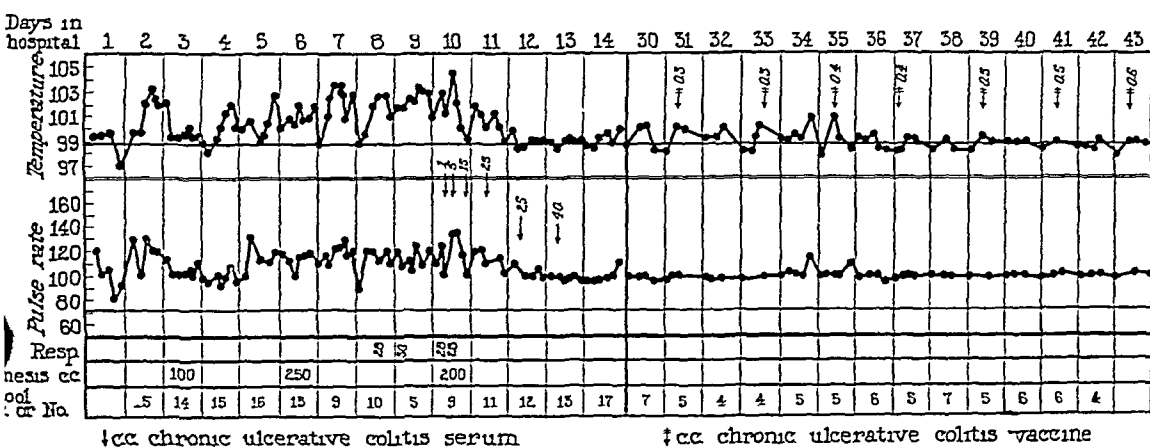


Fig. 3 (case 4) —Portion of the hospital chart, showing temperature and pulse curve, decrease in evacuations from the bowel and gain in weight following the use of immune serum.

The leukocytes on two occasions numbered 10,400 and 14,200. The proctoscopic examination resulted in a diagnosis of chronic ulcerative colitis, graded 2+. The wall of the bowel showed uniform involvement, with contraction to about a third of its normal diameter. The roentgenogram of the colon by barium enema showed that the colon was narrowed and nonhausted up to the splenic flexure, indicating that the disease involved at least that portion of the large bowel from the anus to the splenic flexure.

The patient appeared ill and was admitted to the hospital where she remained for thirty-six days. The rectal discharges ranged between fourteen and twenty-four in twenty-four hours. She improved gradually and was dismissed October 5, she had gained weight and was feeling better. The discharge had decreased in frequency.

After a week at a boarding house she contracted acute pharyngitis and rhinitis, with fever, followed by severe abdominal distress and a great deal more blood in the stools. She was again admitted to the hospital and during the next ten days was extremely ill (fig. 3). The number of discharges from the bowel increased,

abdominal pains were severe, and the fever ranged between 102 and 104.5 F daily. The hemoglobin was 55 per cent, erythrocytes numbered 3,330,000 and leukocytes on two successive counts numbered 15,200 and 22,900, with 79 and 71 per cent polymorphonuclear neutrophils. Results of a roentgen-ray examination of the chest were negative, as were those of repeated urinalyses. The Widal test was negative. Repeated tests of the stools for acid-fast bacilli were negative. Nothing unusual was observed except the grave illness and the acutely tender, flaccid abdomen. Ileostomy was considered on the ninth day after admission, but the idea was abandoned.

On the tenth day a positive blood culture of the diplococcus of chronic ulcerative colitis was obtained, and serum treatment was begun immediately. The first injection consisted of 1 cc given intracutaneously as a desensitizing dose. Two hours later, 5 cc was injected deeply into the muscle, six hours later, 15 cc, twenty-four hours later, 25 cc, twenty-four hours later, 28 cc, and twenty-four hours later, 40 cc. Twenty-four hours after injections on the first day, the temperature dropped to normal and during the following two weeks did not rise above 100.5 F, the last six days in the hospital the temperature was about normal. The discharges from the bowel gradually decreased so that on dismissal, November 13, they averaged four in twenty-four hours. The rectal discharge had not contained blood for ten days. The last ten days the patient gained 7.5 pounds (2.9 Kg) and was feeling well.

Nine days after the last injection of serum, 0.1 cc of an autogenous sensitized vaccine prepared from the diplococcus isolated from the patient's blood was given subcutaneously, and thereafter until dismissal an injection was given every third day. On November 28, the tooth with a periapical abscess was removed with aseptic precautions. Culture of the abscess yielded a diplococcus morphologically and biologically like that obtained from the blood during the severe illness. When this was injected intravenously into two rabbits, acute ulcerative colitis developed in one and marked diarrhea in the other.

Besides the treatment with immune serum during the acute exacerbation of the chronic ulcerative colitis and with sensitized vaccine later, a focus of infection was removed, and a high-caloric, low-residue diet was prescribed, which was gradually increased to a liberal, nourishing diet.

CASE 5—A man, aged 59, came to the Mayo Clinic on April 2, 1926, with a history of a duodenal ulcer dating back to 1916 or 1917, which had been fairly well controlled by medical treatment. Three and a half months previously, he had begun to have watery diarrhea which had gradually changed to passages of mucus and pus, a maximum of eight passages in twenty-four hours. He had lost 30 pounds (13.6 Kg) in weight. The blood counts were essentially normal except for 5,000 leukocytes, of which 48.5 per cent were neutrophils. Gastric analysis after a test meal showed total acid 60 and free acid 48, the amount was 30 cc. The Wassermann reaction of the blood was negative. Results of urinalysis were negative. Acid-fast bacilli were not found in the stools or smears of the rectal ulceration. In three tests of the stools, on as many mornings, parasites or ova were not found. A dead tooth was found, and the tonsils were slightly enlarged. Proctoscopic examination showed the typical picture of chronic ulcerative colitis. A roentgenogram of the stomach showed a duodenal ulcer. A roentgenogram of the colon showed that the process involved the entire colon. Repeated attempts failed to isolate the diplococcus through the proctoscope.

The dead tooth was removed on April 13, and tonsillectomy was performed on April 26. A diplococcus was isolated of the morphology of those usually found in the rectum, which was agglutinated by the horse serum, and a vaccine was

prepared The patient was given an autogenous filtrate, and he gradually improved Alternating with the autogenous vaccine, he was given a mixed filtrate so that when he was dismissed June 10, 1926, he was getting 15 cc of each alternately He also received tincture of iodine, 10 drops to a dose, one week in every three, and kaolin as necessary He continued treatment with vaccine at home and gradually improved until about the middle of November, when he became worse and was given four injections of neoarsphenamine (0.9 dg) After the second injection, he was definitely better, but from then on he became steadily worse The injections were given once a week By the end of February, 1927, bloody stools averaged from twenty to twenty-five in twenty-four hours, and these were accompanied by fever and all the symptoms of a severe acute exacerbation of chronic ulcerative colitis The proctoscope confirmed this At this time the usual diplococcus was isolated which was agglutinated in high dilutions by the serum of the two horses immunized He was given 1 cc of the immune serum (concentrated) intracutaneously and two hours later 10 cc On the four successive days, he was given 20, 30, 40 and 50 cc of the serum deep in the muscle Within a week the number of stools had reduced to eight or ten in twenty-four hours, and the blood gradually stopped Then he had a severe serum sickness in the form of urticaria, which lasted ten days A fresh vaccine was prepared from the organism isolated from the rectal ulcers, and this was given in gradually increasing doses The proctoscope on April 14 showed activity graded 2 + The patient gradually improved, receiving, besides the vaccine, gentian violet in tablet form, alternating with tincture of iodine and bismuth subnitrate as necessary He was dismissed on July 25, the average number of stools was about six a day and he had gained considerably in weight In a general way he was feeling much improved In a letter written on October 1, he stated that he was still slowly improving The form of treatment after his dismissal consisted of administration of the autogenous vaccine at regular intervals, alternating with gentian violet and tincture of iodine

CASE 6—A woman, aged 21, came to the Mayo Clinic on Dec 10, 1924, with a history of abdominal pain of five months' duration, so severe that it doubled her up The pain was followed by loose stools mixed with bright red blood There were between six and seven discharges during the day and several at night In the five months, she thought that there was blood in every stool The pain was constant and described as tearing, with griping when stools were passed, and was worse after meals There had not been fever or chills She had lost 10 pounds (4.5 Kg) The symptoms had grown worse during the last three weeks On admission the blood count and the urine were essentially normal The Wassermann reaction of the blood was negative The proctoscope showed ulcerative colitis, beginning in the sigmoid, the first 20 cm of the rectum being essentially normal A roentgenogram of the colon showed a lesion of the colon, from the cecum to the sigmoid, and chronic ulcerative colitis was diagnosed Because of the possibility of tuberculosis, exploration was advised Acid-fast bacilli were not found in the stools, and a culture was not made

On Dec 29, 1924, ileostomy was performed for chronic ulcerative colitis, it was suggested that ileosigmoidostomy might be performed later, as the sigmoid seemed normal The patient gradually recovered, went home and was fairly well until June, 1925 On Sept 1, 1925, she returned with a history of gradual failure and four severe rectal hemorrhages, four days previously The hemoglobin at this time was 60 per cent The roentgenologic diagnosis was chronic ulcerative colitis The proctoscope showed the sigmoid full of thick, bloody pus Colectomy was performed on September 3, the pathologic diagnosis was polyposis of the

cecum ascending colon and part of the transverse colon. An abscess developed later in the abdominal cavity and was drained on October 7. The patient was dismissed on December 16 improving, and was given some vaccine to take at home. She returned on Oct 19, 1926, at which time the proctoscopic picture was that of chronic ulcerative colitis, the activity of which was graded 1+. She was sent home again and given more vaccine. She returned Feb 15, 1927, at which time the mucosa seemed to be in good condition, and she stated that she had not had symptoms for months. There was no discharge from the rectum except by irrigation (which she carried out from one to three times a week). She had gained 40 pounds (18.1 Kg) in the year since the last operation. Ileosigmoidostomy was performed on Feb 24, 1927. She left the clinic March 22 in splendid condition. She returned eight days later suffering from an acute exacerbation of the colitis which included the rectum and sigmoid, and extended into the ileum, and during the following five days was given 15, 20, 30, 30 and 40 cc of the immune serum of chronic ulcerative colitis. Before this her temperature had ranged between 101 and 102 F, and there were many bloody rectal discharges. There was a

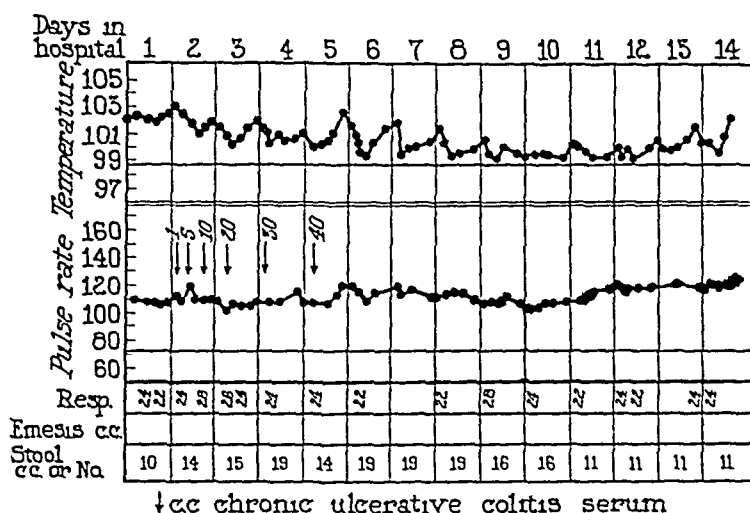


Fig 4 (case 7) —Portion of hospital chart

definite decrease in the amount of blood in the stools and in the number of stools after the serum was administered, and improvement continued for a week. From April 4 to 12, she suffered from a severe serum sickness, with temperature as high as 102 F, accompanied by severe urticaria. She gradually improved until September 1, from this time on, however, failure was progressive and she died September 21. This case is another illustration of the futility of ileosigmoidostomy for chronic ulcerative colitis.

**CASE 7**—A woman, age 37, was brought to the hospital in an ambulance Dec 29, 1927, with a history of bloody diarrhea of ten years' duration. During the four months previous to admission, the condition had been unusually severe, confining her to bed. She had lost 13 pounds (5.9 Kg) in four months. Rectal discharges occurred three or four times every hour and could not be controlled. The proctoscopic examination revealed the usual picture of chronic ulcerative colitis. A roentgenogram showed involvement of the entire colon. The temperature was 103 F. The hemoglobin was 56 per cent, the erythrocytes numbered 3,540,000 and the leukocytes 9,900.

From January 1 to 4, the patient (fig 4) was given successively 1, 5, 10, 20, 30 and 40 cc of the immune serum of chronic ulcerative colitis. The first three injections were given on the first day, the first intracutaneously, the others deep muscularly. By January 8, the temperature had dropped to 99.5 F and varied



between 99 and 100 F until a transfusion was given on January 13. Several days after the transfusion the symptoms again receded. The number of stools dropped to an average of ten in twenty-four hours until January 27, when a subacute perforation developed. The course was then stormy for ten days. At the end of this time the temperature receded. On February 15, vaccine treatment was begun. The patient was dismissed on March 18, the temperature had been normal for a week, there were seven stools in twenty-four hours, and she was gaining weight and was generally improved. Further treatment consisted of the use of vaccine and a nourishing, high-caloric and high-vitamin diet, improvement has been progressive.

#### COMMENT

In all cases in which the serum was given, there was definite improvement in the general condition. The increase in weight soon after institution of treatment with serum is significant. The serum seemed to have definite neutralizing power of the toxin of the organism causing chronic ulcerative colitis. The effect on the temperature and pulse curves is noteworthy. The outstanding improvement as shown by the proctoscope and by roentgenograms of the colon by barium enema, is of the greatest significance.

The immunization of horses is being continued. Better results are anticipated for the future. The results in this small series of almost hopeless cases are encouraging. They suggest that the present method of treatment is in the right general direction. At least two of these cases illustrate the futility and impracticability of ileosigmoidostomy in the treatment of patients with chronic ulcerative colitis.

# THE RELATION OF THE HIATUS ESOPHAGEUS OF THE DIAPHRAGM TO THE STOMACH

AN IMPORTANT FUNCTION OF THE PILLARS OF THE DIAPHRAGM<sup>1</sup>

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CHICAGO

The most commonly recognized function of the diaphragm is the part it plays in the mechanism of inspiration and expiration. The diaphragm also acts as a dividing membrane that forms the floor of the chest cavity and the roof of the abdominal cavity. When in tone, the diaphragm prevents the abdominal viscera from being pushed into the thoracic cavity. It also acts as a pressor muscle during the acts of defecation and parturition.

The function that has been least emphasized and only recently recognized is the constrictor action of the muscle at the gastro-esophageal junction. It was first described by Chevalier Jackson, and was called by him and his associates<sup>1</sup> a pinch cock effect. I<sup>2</sup> first encountered this phenomenon about four years ago during the course of certain experiments on the lung by using the transdiaphragmatic extraperitoneal route. Under certain conditions I encountered an acute distention of the stomach which caused a prompt death to the animal used in the experiment. Such a dilatation was frequently encountered during an operation on the lung when there was an undue amount of unnecessary manipulating of the lung. I also noticed a dilatation in cases in which there was rough manipulation and an excessive amount of downward retraction of the diaphragm, in cases in which an operation was performed on the lung with a preliminary resection of the phrenic nerve at the beginning of the operation, and finally in a few cases of prolonged deep anesthesia when a positive pressure artificial respiration was used with or without an open pneumothorax. Whenever the stomach became acutely distended, air could easily be pumped into the stomach, but it was difficult to remove this air even after a great amount of pressure was exerted over the walls of the stomach. Little if any air escaped from either the pyloric or the cardiac end with ordinary squeezing of the walls of the stomach. If, on the other hand,

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<sup>1</sup> From the Department of Surgery, University of Illinois College of Medicine

1 Tucker, G. Diaphragmatic Pinch Cock in Health and Disease, *M. Clin N Amer* 8 931, 1924

2 Joannides, M. An Extraperitoneal Intrapleural Route of Approach for Intrathoracic Surgery, *Ann Surg* 80 908, 1924, 84 337, 1926

a tube was inserted into the stomach, the air would escape easily and promptly. I decided, therefore, to study this phenomenon rather carefully.

In my study of the anatomy of this region, I was disappointed because I found that the descriptions of the relation of the hiatus to the esophagus were entirely different from what I found this relationship to be in the dog. Believing that there may be variations in the anatomy of the dog from that of man, I studied this relationship also in the human being and found that with few exceptions my observations on the dog were similar to those on the human cadaver. In the illustrations in

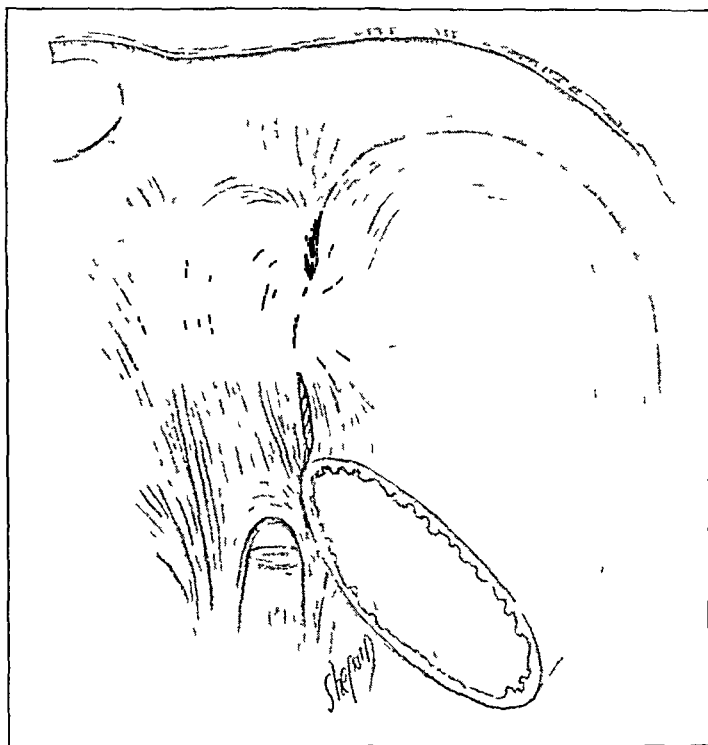


Fig 1—Dissection of the pillars, showing the relation of the fibers to the stomach

textbooks, the hiatus esophageus is ordinarily so placed that one notices at least 1 cm. of the esophagus below the diaphragm. In my study of this relationship in the dog as well as in the cadaver I found that the hiatus esophageus is located at the level of the gastro-esophageal junction. I also have noticed that in the dog the relationship between the fibers of the pillars and those of the gastro-esophageal area is much more intimate than that in the human being. In the latter there is usually a layer of fibrous tissue that separates the fibers of the pillars from the stomach and esophagus. On the other hand, in the dog this fibrous layer is extremely thin so that one receives the impression that the fibers of the pillars are in apposition with those of the stomach

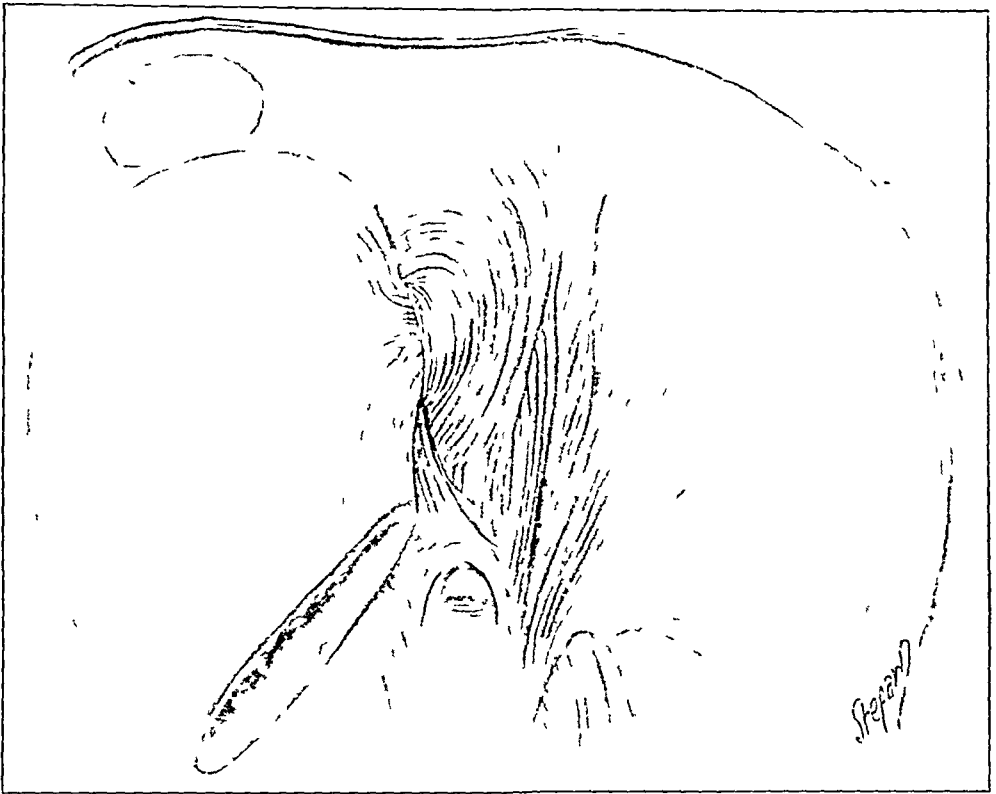


Fig 2—Stomach pulled to the right to show the direction of the fibers



Fig 3—Dissection of the lesser peritoneal cavity Note the fibers of the right pillar as they show through the peritoneum

(figs 1, 2 and 3) Anteriorly the fibers of the pillars surround the stomach and the esophagus in a manner similar to that of the fibers of the anal sphincter. As they go posteriorly, they decussate and are attached to the vertebrae. The fibers of the pillars also form more or less the posterior layer of the lesser peritoneal cavity at the region of the vertebrae. In some instances, I have found on the posterior surface of the stomach a small triangle the sides of which are made up by the fibers of the pillars and the base by the posterior wall of the esophagus and the stomach. The size of the triangle varies in different subjects. In the dog it is usually small and at times absent, in man it is larger and measures from 1 to 2 cm in length. The sides of the triangle are jointed together by means of fibrous tissue so that at times one may be able to admit an index finger through this potential opening.

In order to study the functional mechanism of these pillars and the parietal diaphragm, I made a gastrostomy and through that I inserted my finger into the esophagus. With the finger in this position, I noticed that coincident with each respiratory movement I could feel a

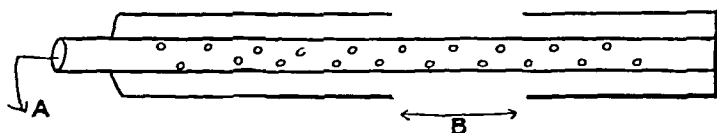


Fig 4—Diagram of tambour for recording diaphragmatic contractions. *A* indicates opening to recording tambour and *B*, the area covered with rubber finger.

progressively downward constriction at the site of the pillars. These contractions gave one the impression of milking contractions. With deeper respirations and when the animal strained, this milking effect became more evident. In order to determine whether or not this contraction was independent of the esophageal contractions, I paralyzed the diaphragm and noticed that these milking contractions stopped. By stimulating the vagus nerve peripherally or the esophagus I could get a contraction, but this time an entirely different type. This contraction was of the constricting type without any downward effect.

In order to determine whether or not the whole diaphragm was responsible for the milking effect or just the pillars, I stimulated the phrenic nerve at various levels and noticed a massive downward movement of the peripheral portion and, to a less extent, the central portion of the diaphragm. As a result of this contraction, the whole stomach and the liver were pushed down. When, on the other hand, the fibers of the pillars were stimulated directly from either the thoracic or the abdominal side, I noticed the characteristic milking contraction.

Under no circumstances could any contractions be induced if any portion of the cardiac end of the stomach was stimulated. By this

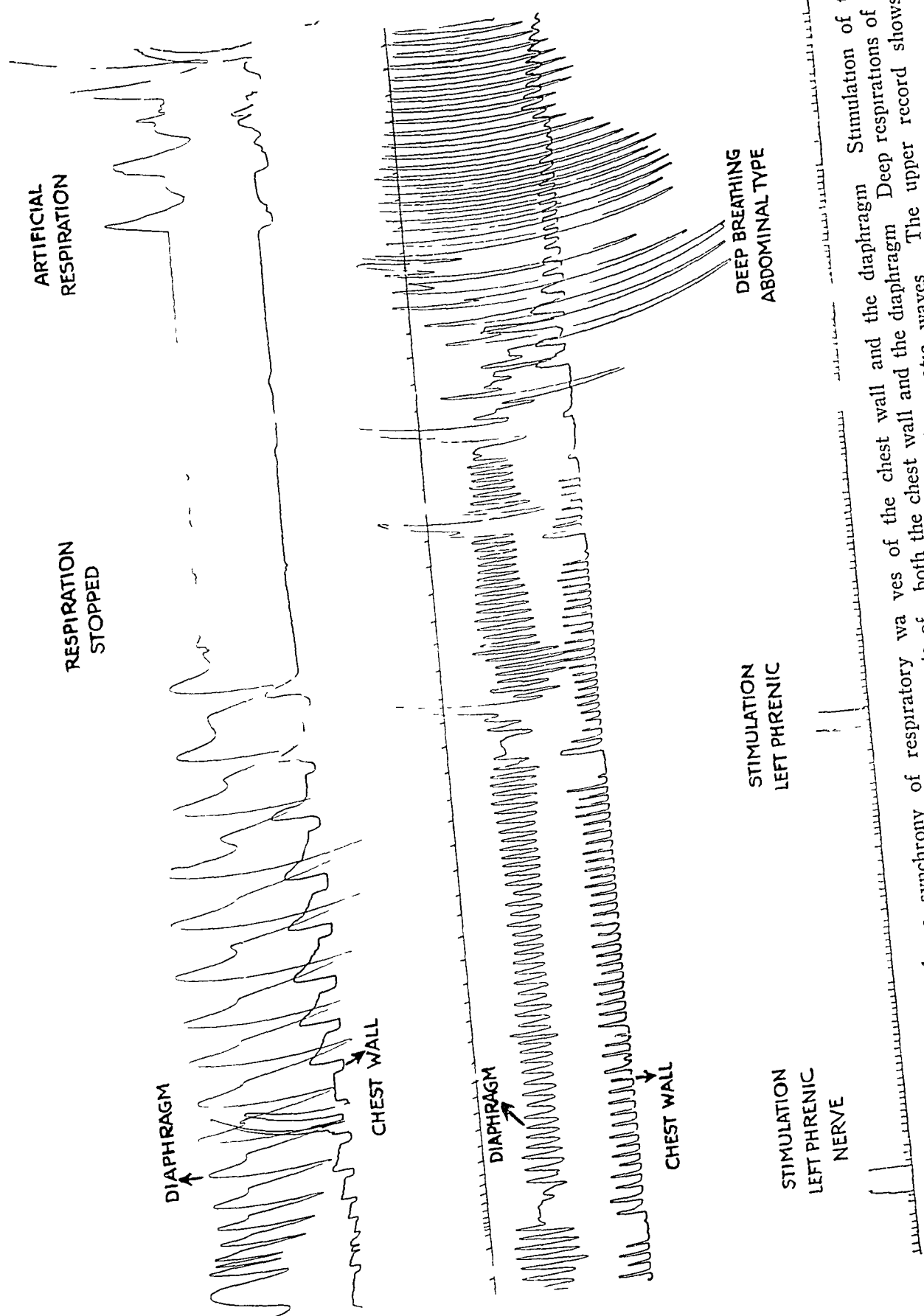


Fig 5—Lower record shows synchrony of respiratory waves of the chest wall and the diaphragm. Stimulation of the phrenic nerve shows a momentary cessation of the movements of both the chest wall and the diaphragm. Deep respirations of the abdominal type show the corresponding change in the amplitude of the diaphragmatic waves. The upper record shows a synchronous cessation of the waves of the chest wall and diaphragm when the respiration stopped.

means I could determine accurately the exact location of the esophageal-gastric junction. Stimulation of the esophagus up to the point of the junction would induce the characteristic contraction of the constricting type. Stimulation distal to the junction would not produce any effect.

In the next series, I tried to inflate the stomach by inducing a pharyngeal artificial respiration under otherwise normal conditions. I was unable to produce the acute distention that I encountered in cases in which operations on the lung had been performed. I also failed to produce distention even when I inserted an esophagoscope and pumped

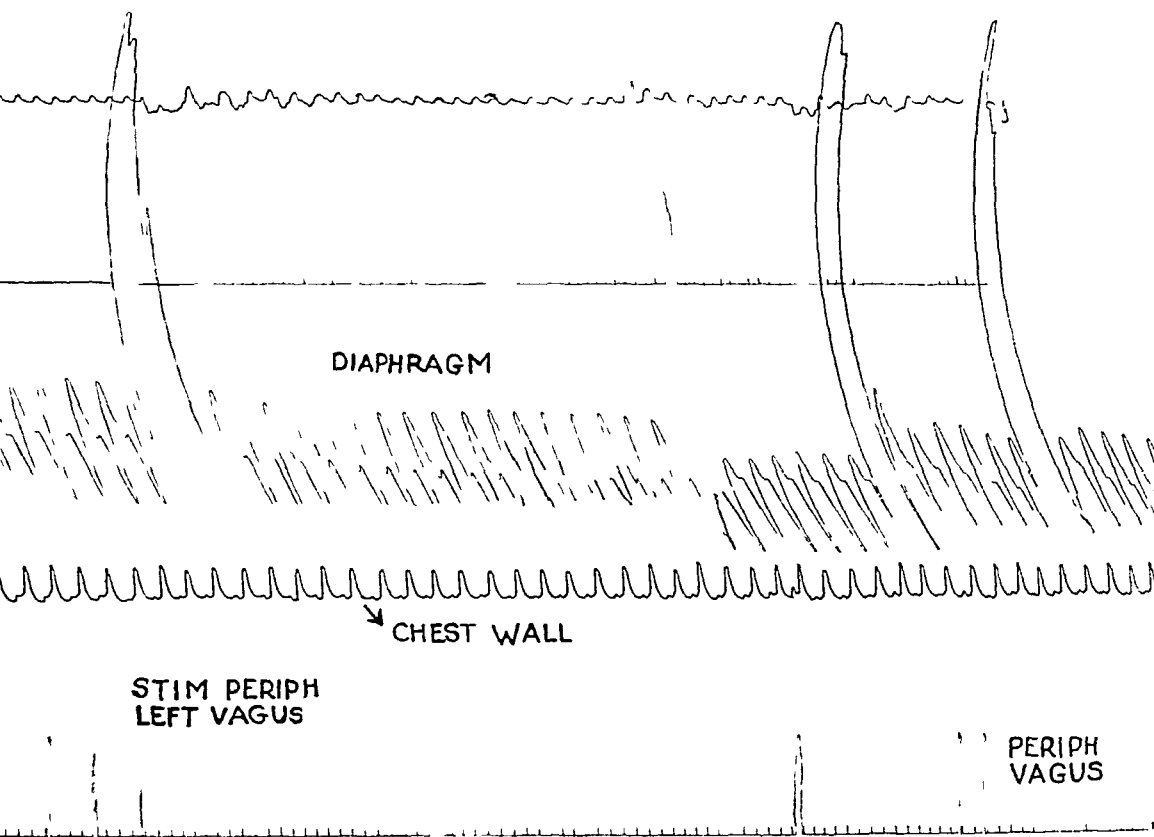


Fig 6—Stimulation of the peripheral end of the vagus nerve shows the effects of the constricting contraction of the esophagus without inducing any change on the waves of the chest wall

compressed air into the stomach. If, however, the diaphragm, the lungs or the phrenic nerve was manipulated under conditions already mentioned, an acute dilatation of the stomach promptly developed. When the stomach is distended under these conditions, little air escapes from either the cardiac or the pyloric end, with the result that the stomach becomes tense and drumlike. On opening the duodenum just beyond the pylorus it was noticed that little if any air escaped from that end. At the cardiac end the air could escape with less difficulty, but not until an esophagoscope was inserted could free escape of the air be noted.

This last observation leads one to believe not only that the sphincter action of the pillars at this junction is of the milking type, but that because of the peculiar shape of the diaphragm there is a one way valve effect so that contents entering the stomach cannot easily be squeezed out

In order to obtain exact and permanent records of these contractions, I devised an oblong tambour which can be inserted into the esophagus at the hiatus and thus record these contractions. This tambour (fig 4) was constructed by inserting one brass tube into another and so arranging the rubber dam that the contractions would be transmitted to a second tambour and thence to the kymograph. By this means, I was able to notice to my own satisfaction that the contractions at the hiatus were homologous and synchronous with the excursions produced by a pneumograph that records movements during expansion of the chest. One could easily use this method for recording respiratory movements by making a gastrostomy and inserting the pneumograph into the gastro-esophageal junction (figs 5 and 6)

#### SUMMARY

1 There is an intimate relationship between the pillars of the diaphragm at the hiatus esophageus and the gastro-esophageal junction

2 The pillars exert a milking contraction on the gastro-esophageal junction and thus prevent the gastric contents from spilling backward into the esophagus

3 The milking contraction is observed after stimulation of the pillars of the diaphragm or after stimulation of the trunk or the branches of the phrenic nerve in the immediate neighborhood of the pillars

4 Stimulation of the vagus nerve or the esophagus produces a circular constriction at the gastro-esophageal junction. Stimulation of the vagus on the abdominal side or stimulation of the cardiac end of the stomach does not result in any contraction at the junction

5 An acute dilatation of the stomach was encountered with the following conditions (1) at the end or during a lobectomy or pneumectomy when there was an undue amount of rough handling of the lung, (2) as a result of unnecessary handling of the diaphragm, especially after downward retraction of the muscle, (3) in operations on the lung during which a resection of the phrenic nerve was made at the beginning of the operation, and (4) in a small number of cases of prolonged deep anesthesia when shock occurred or when there was a pharyngeal type of artificial respiration with positive pressure



# NORMAL RHYTHM OF WHITE BLOOD CELLS IN WOMEN \*

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This study was made to determine whether or not the physiologic process of menstruation may influence the regular daily rhythm of the white blood cells, which has been shown to exist independently of other physiologic factors such as digestion and ordinary exercise (Sabin, Cunningham, Doan and Kindwall,<sup>1</sup> 1925, and Shaw,<sup>2</sup> 1927) The results obtained by these authors in regard to the effect of digestion were confirmed, and it was further found that menstruation does not appreciably affect the rhythm of the white blood cells, although there is a lymphocytic and leukocytic infiltration of the endometrium preceding the onset of menstruation (Novak and Te Linde,<sup>3</sup> 1924) This is taken as indicating that this rhythm is an essential characteristic of the white blood cells and is one phase of the fundamental rhythmicity of the vital activities of the body

In the course of this investigation, it was found that a type of cell identified as a young eosinophil was present, which was basophilic in reaction and which was closely allied to the lymphocytic group of blood cells

## METHODS

Data regarding variations in the number of the white blood cells were obtained from two persons, five series of counts being made on each Three of the series in the case of subject A and two in the case of subject B consisted of the first three days of menstruation The third series of subject B included the day preceding the onset of menstruation and the first three days of menstruation The fourth series in both cases included two consecutive days in an intermenstrual period, and the fifth was a series taken during menstruation when meals were omitted The fifth series consisted of the first day of menstruation in the case of subject A, and of the first three days in the case of subject B

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1 Sabin, F R , Cunningham, R S , Doan, C A , and Kindwall, J A Bull Johns Hopkins Hosp **37** 14, 1925

2 Shaw, A F B J Path Bact **30** 1, 1927

3 Novak, E, and Te Linde, R W Endometrium of Menstruating Uterus, J A M A **83** 900 (Sept 20) 1924

In one case (April 17, 1927, during menstruation), a count was made while the subject had an attack of gastro-enteritis. Food, except in the fifth series, and water in all series were taken as in ordinary daily life. Breakfast on some days was omitted, on others it was eaten between one-half hour and ten minutes before the first count was made. Lunch was eaten between four and six hours after the beginning of the count. On some days, food in small quantities was eaten occasionally. Both subjects took an active part in the counting and technical work involved in the experiments, and a moderate amount of exercise, as in ordinary daily life, was taken in all cases. In all, there are counts for twelve days on subject A and for fifteen days on subject B.

The methods used were essentially those described by Sabin, Cunningham, Doan, and Kindwall,<sup>4</sup> with minor modifications. Total and vital differential counts were made at fifteen or twenty minute intervals, for eight hour periods. Total counts were made with U S standardized pipets. The half-per cent acetic acid used for diluting the blood was made each morning before the counts were begun. Two of the workers alternated in making the total counts and the vital differential counts, but in all series the same person made total counts on one subject to eliminate the personal equation as far as possible. One of the persons made vital differential counts throughout. Fixed smears for differential counts were made at the same time that blood was taken for the total and the vital differential counts. From 200 to 250 cells were counted on the fixed smears. The vital preparations were made according to the technic described by Cunningham, Sabin, Sugiyama, and Kindwall<sup>4</sup> (1925), and 100 cells were counted on each slide.

#### TYPES OF WHITE BLOOD CELLS

In this study, the white blood cells which have been seen have been classified into four main groups: polymorphonuclear leukocytes, lymphocytes, monocytes and endothelial cells. The leukocytes have been further divided into neutrophils (both active and nonmotile), eosinophils and large and small basophils. The lymphocytes have been divided into small, intermediate, large and stimulated. The cells have been found to follow closely those described by Sabin<sup>5</sup> (1923), so that only those are discussed in this paper in which differences have been noted, or where it has been thought that more emphasis should be given to certain details.

*Nonmotile Leukocytes*—In studies on both supravital and fixed preparations of blood, Sabin, Cunningham, Doan and Kindwall<sup>4</sup> have observed that nonmotile cells occur at times in large numbers. They have found such "showers" of nonmotiles both in heart's blood (rabbit) and in peripheral blood (human, finger, rabbit, vein of the ear). Their conclusion is that the neutrophils die in the circulation in great numbers, and that "these showers of nonmotile or dying cells represent a most important factor in the physiology of the blood."<sup>6</sup>

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4 Cunningham, R. S., Sabin, F. R., Sugiyama, S., and Kindwall, J. A. Bull Johns Hopkins Hosp 37 231, 1925

5 Sabin, F. R. Bull Johns Hopkins Hosp 34 277, 1923

6 Sabin (footnote 1, p 51)

In the present study, nonmotile cells have been seen in good smears but more often in poor ones. Occasionally a nonmotile is found on the same field with an active neutrophil or on the next field, and such cells have been considered neutrophils which have died in the circulation. However, marked showers were not observed. Nonmotile cells are rare on fields in which active cells are present and in which there is room for active movement. They have generally been found in thin places in an uneven smear or in the thin smears which result from using too small a drop of blood. These observations lead us to the conclusion that nonmotile cells result more often from technic and less often as neutrophils dying in the circulation.

*Basophils and Eosinophils*—The significance of the basophil is a much disputed point. Numerous investigators regard it as a specific cell of equal rank with the other two types of granular leukocytes (Downey,<sup>7</sup> 1914, Ringoen,<sup>8</sup> 1915, Bunting,<sup>9</sup> 1922, Maximow,<sup>10</sup> 1924, Sabin, Cunningham, Doan and Kindwall<sup>1</sup>). On the other hand, many authors believe the basophil to be a degenerate or immature form of one of the other types of white cell. The question is complicated by the fact that eosinophilic granules may pass through a basophilic stage, and the question arises whether the basophils of the blood are these immature eosinophilic cells or whether they possess specific granules of different origin. Weidenreich<sup>11</sup> considered that they are degenerate lymphocytes in most animals. The negative peroxidase reaction of the basophilic granules correlated with progressive degenerative nuclear changes is interpreted by Graham<sup>12</sup> (1920) as indicating that the basophil is a degenerate eosinophil or, rarely, a neutrophil. Doan and Sabin<sup>13</sup> (1926), however, did not draw the same conclusion from this fact. Sometimes Graham found cells in which some of the granules reacted positively and the rest negatively, or in some cases the individual granules gave a mixed reaction, that is, the center reacted positively and the periphery negatively to the peroxidase test. This metachromatic reaction is of especial interest in view of a recent paper by Jordan<sup>14</sup> (1926).

From studies on fixed material of frog and teleost intestine, Jordan<sup>14</sup> classified the tissue basophils of the mucosa according to whether the granules stain blue (orthobasophilic) or purple (metachromatically basophilic) in Giemsa stain. The cells with orthobasophilic granules are

7 Downey, H. Abstr. in Anat. Record **8** 135, 1914

8 Ringoen, A. R. Anat. Record **9** 233, 1915

9 Bunting, C. H. Physiol. Rev. **2** 505, 1922

10 Maximow, A. A. Physiol. Rev. **4** 533, 1924

11 Weidenreich, F. Anat. Record **4** 317, 1910

12 Graham, G. S. J. Exper. Med. **31** 209, 1920

13 Doan, C. A., and Sabin, F. R. J. Exper. Med. **43** 839, 1926

14 Jordan, H. E. Anat. Record **33** 89, 1926

thought to be immature eosinophils which develop from connective tissue cells. As they mature, the granules gradually become acidophilic and react somewhat to the eosin, presenting a metachromatically basophilic (purple) appearance. If at any time in this process of maturation degenerative or abortive changes occur, the granules also become metachromatic. When mature, the granules stain in eosin with no trace of blue. Although a contrary view is held by many authorities (Bunting<sup>9</sup>), Jordan does not believe the tissue basophil to be sharply distinct from that of the blood, and consequently his observations on the one are applied to the other. Jordan and Speidel<sup>15</sup> found that eosinophils develop by way of an intermediate basophilically granular stage from lymphocytes or connective tissue in amphibians and fish. Further evidence that eosinophils may be derived from hemoblasts is presented by Latta<sup>16</sup> (1921) in a study of the tonsil of the rabbit.

In the present study of human blood, two types of basophils have been found. The first is a large cell which is apparently the type referred to by Sabin<sup>1</sup> as an actively functioning cell, and by Graham<sup>12</sup> as a degenerate eosinophil or, rarely, a neutrophil. The granules of the large basophil are spherical and vary in size between those of neutrophils and eosinophils, they are acidic, since they stain a deep, slightly purplish red in vital neutral red, and bluish to reddish purple in Wright's stain. Basophils have not often been seen in motion. When they do move, it is with an ameboid motion, the granules going ahead of the nucleus.

The small basophil seen in the living state is quite different in appearance and behavior from the large basophil and probably belongs to a totally distinct group both in mode of origin and in later development. The study of this cell demonstrates strikingly the advantage of the supravital method of studying cells over the fixed-smear method, since in fixed smears it is entirely similar to the large basophil except in size. In numbers they have been found to vary from 0 to 4 per cent of the white cells, the average percentage being 0.6.

In vital preparations, it is a small actively motile cell which moves mainly by a streaming of the protoplasm, although sometimes clear lobate pseudopodia have been seen at the posterior end. In old or overheated preparations this cell may become round and motionless, as do other cells under the same conditions. When the cell is active, the nucleus moves ahead of the main body of cytoplasm, sometimes a few granules dart about in front of the nucleus. The nucleus is similar to the deeply indented nucleus sometimes seen in lymphocytes, at times it appears bilobed. The granules are spherical and vary in size from tiny specks

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<sup>15</sup> Jordan, H. E., and Speidel, C. C. *Am J Anat* **32** 155, 1923, **33** 485, 1924. Jordan (footnote 14).

<sup>16</sup> Latta, J. S. *Am J Anat* **29** 159, 1921.

to bodies almost as large as the granules of an eosinophil. They do not react uniformly to neutral red, since in some cells they are deep red and not refractive, while in others they are lighter. More often the periphery takes the deep maroon color of basophilic granules, while the center is lighter. Such granules are often refractive when the focus is at the periphery or above the cell. They are believed to be similar to the metachromatic granules of Jordan's<sup>17</sup> developing eosinophil. Their appearance is much like that of Graham's<sup>18</sup> peripherally stained metachromatic granule, which however, he called degenerate instead of immature. Again, the granules sometimes resemble those of the eosinophil in color and refractivity. However, in spite of the differences in granules exhibited by individual cells in supravital preparations, these small cells surely belong to one group. Such cells do not contain mitochondria and are not phagocytic, since vacuoles are not present.

In fixed smears these cells appear as small basophils with metachromatic (purple) granules and but for their small size might be confused with ordinary large basophils. The evidence seems to indicate that these small cells are stages in the development of eosinophils from lymphocytes. Their close relationship to the lymphocytic group seems clear, since they move with the nucleus ahead, as do lymphocytes, and the nucleus itself resembles the lymphocytic nucleus. Such cells also may have clear hyaline pseudopodia. The lack of mitochondria is probably due to their disappearance before the maturing eosinophil reaches the peripheral circulation.

The question of the specificity of the types of white blood cell will not be discussed in this paper. A discussion of the leukocytes by Bunting,<sup>9</sup> together with recent articles by Maximow<sup>10</sup> and Jordan,<sup>14</sup> who support the monophyletic theory of blood cell origin, and by Cunningham, Sabin and Doan<sup>19</sup> (1925), who uphold the dualistic or polyphyletic theory, have appeared. The facts already presented indicate that eosinophils may differentiate from lymphocytes, although they, like the other granulocytes, have been considered myelocytic in origin. This apparent double origin of eosinophils is one argument against strict specificity of the white blood cell groups.

*Lymphocytes*—Sabin's classification of lymphocytes into small, intermediate and large has been followed, except that in vital studies the large and intermediate forms with increased phagocytic activity have been classified separately as "stimulated lymphocytes" (Cunningham, Sabin and Doan,<sup>19</sup> Sabin<sup>5</sup> and Sabin, Cunningham, Doan and Kindwall<sup>1</sup>).

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17 Jordan (footnote 14, p 101)

18 Graham (footnote 12, fig 7)

19 Cunningham, R S, Sabin, F R, and Doan, C A. Contribution to Embryol no 84, Carnegie Inst, Washington 16 229, 1925

Stimulated lymphocytes differ mainly from the ordinary large and intermediate forms in having the cytoplasm crowded with neutral red vacuoles which are smaller than the vacuoles of neutrophils and monocytes. They are of two general types. The first kind closely resembles a monocyte in having a bean-shaped nucleus and neutral red vacuoles clustered in the indentation of the nucleus. It might be confused with a monocyte in which the roset arrangement of natural red granules and vacuoles around the centrosphere is obscured by the movement of the cell, or by an increased number of vacuoles, except that the mitochondria of lymphocytes are intermingled with the red-staining vacuoles, whereas in the monocyte the mitochondria are always peripheral to the roset of granules and vacuoles. The second type of stimulated lymphocyte has a lobed nucleus. If the vacuoles become numerous, the mitochondria may be obscured, and at first the beginner may confuse the cell with a basophil. Stimulated lymphocytes in fixed smears appear as ordinary large or intermediate lymphocytes. The stimulated lymphocyte is particularly mentioned here because it occurs more frequently than the literature indicates, and a knowledge of its structure is most important in the diagnosis of lymphocytes and monocytes. Maximow<sup>10</sup> found similar cells in conditions of inflammation.

Sabin<sup>5</sup> observed large lymphocytes dividing amitotically in the blood stream in a case of lymphoid leukemia. In this study, dividing lymphocytes have been seen occasionally.

*Monocytes*—Monocytes are characterized by a bean-shaped nucleus. They have a peculiar roset of fine granules and larger vacuoles arranged radially about the centrosphere in the *hof* of the nucleus. Mitochondria are present and are always peripheral to the cluster of red-staining bodies. The latter detail of arrangement distinguishes the monocyte from the stimulated lymphocyte, but even this criterion is sometimes difficult to apply, because a monocyte may contain so large a number of vacuoles that the centrosphere is obscured, or the mitochondria may lie above the roset of red bodies near the surface of the cell, and it is only by careful focusing that they are seen not to be intermingled with them. Monocytes do not by any means always show their characteristic structures with diagrammatic clearness.

The monocyte moves by means of an undulating membrane, which, according to Carrel and Ebeling<sup>20</sup> (1926), is similar to that of sarcoma cells, macrophages and monocytes which have been cultivated in flasks. Although this membrane is seen best under the dark field microscope, it has been found that the outline as well as the filiform pseudopodia may be seen in part with direct illumination. Some movement may be detected, although the wavelike motion described by Carrel is not appar-

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20 Carrel, A., and Ebeling, A. H. J. Exper. Med. 44 285, 1926

ent In fact, the undulating membrane has been an aid in diagnosis of cells which might be confused with stimulated lymphocytes

#### VARIATIONS IN THE NUMBERS OF WHITE BLOOD CELLS

*Observations*—Normal Rhythm and the Influence of Menstruation  
Previous studies of the white blood cells have usually included serial counts on different persons or isolated ones on the same person In this investigation, serial counts on consecutive days have been made on two persons While no two curves are identical, certain features are constantly present First, the number of white blood cells is markedly greater in the afternoon than in the morning This increase begins in the later part of the morning Only three exceptions (curve 3-2-27, chart 3, curve 3-25-27, chart 5, curve 5-17-27, chart 6) to this general rule occur in the twenty-seven curves included in this paper In these three curves, the highest points come before 12 o'clock In preliminary work, including eleven curves, an exception was not found Second, there is an approximately hourly rise and fall in numbers of cells, which is independent of, and does not affect, the general tendency toward an afternoon rise Third, the greatest number of cells at any time during the day is approximately twice the lowest number for the same day These observations confirm the three points emphasized by Sabin, Cunningham, Doan and Kindwall<sup>1</sup> in regard to the rhythm of the total number of white cells Fourth, there is often, though not invariably, a fall in the number of cells after the preliminary morning rise and before the height of the afternoon rise This has also been noted by Sabin and her co-workers, in their charts 1A, 5E and 6F<sup>21</sup> and by Shaw<sup>22</sup> There is no detailed correspondence between curves for counts on consecutive days As already stated, no two curves are identical, and rhythms of consecutive days are not any more similar than rhythms of days a week or a month apart

However, each person has a curve of characteristic pattern (compare charts 1 and 2) The counts of subject A are higher than the counts of subject B The lower limit for subject A is from 5,050 to 9,350 cells, while the lower limit for subject B is between 4,025 and 6,132 The upper limit for subject A is from 9,475 to 13,425 and for subject B from 7,505, to 10,425, not including the high number of 11,550 which was reached during an attack of gastro-enteritis or the high count of 13,775 (curve 5-15-27, chart 6) The last curve is quite different from the other curves of subject B, showing much higher counts The count was made on the first day of menstruation, and not any food was taken The counts for the two days following were normal Although the characteristic

<sup>21</sup> Sabin et al (footnote 1, pp 39, 40)

<sup>22</sup> Shaw (footnote 2, p 7)

curves of subject A do not fluctuate more irregularly than do those of subject B, their wider range permits of greater fluctuations, which result in a curve pattern different from that of subject B. It is interesting to note that the individual patterns are constantly exhibited, for example, in curve 3-29-27 (chart 4) the pattern is characteristic for subject A, although the zone of fluctuation is between 9,350 and 13,425 cells. These extremely high numbers did not result from any apparent

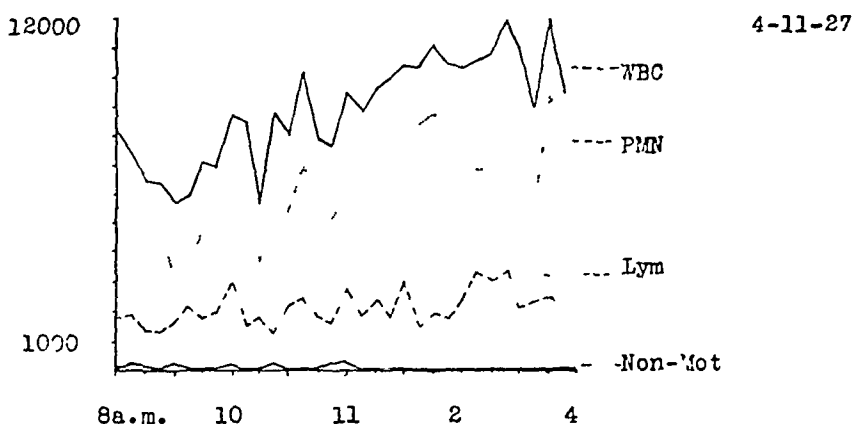
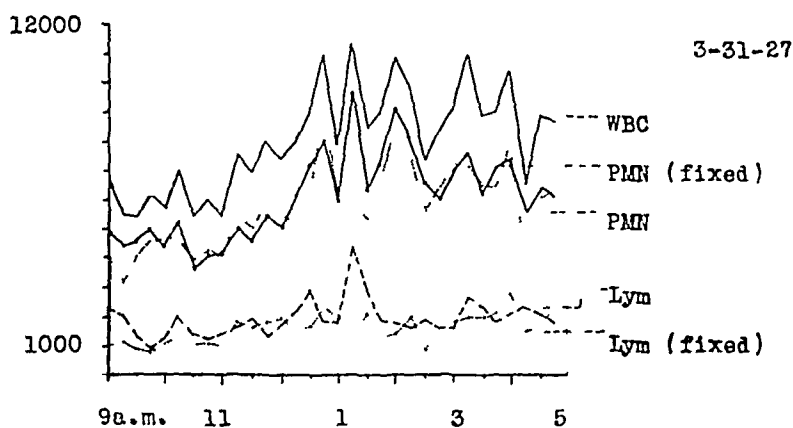
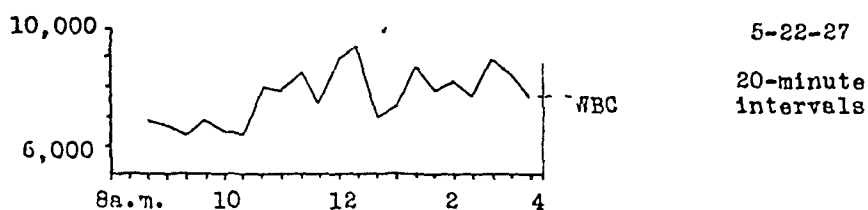


Chart 1—Exact curves of total and differential counts of subject A. Curve 4-11-27 represents a day's count during an intermenstrual period and curves 5-22-27 and 3-31-27 are of counts taken during menstruation. Curve 5-22-27 is for a day when meals were omitted.

The total and differential counts for each day have been plotted graphically (charts 1 to 4) and the curves numbered with the date on which the count was made. The times of day are given on the abscissas and the numbers of cells on the ordinates. *L* indicates lunch and *B*, breakfast, and the figures beneath the date of the curve indicate the time when breakfast was taken. The vertical lines drawn through the curves show when food in small quantities was eaten (candy, crackers, etc.). The vital stain was used unless otherwise stated.



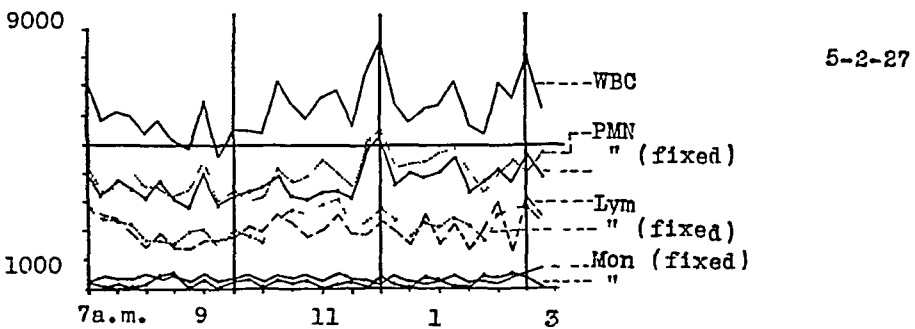
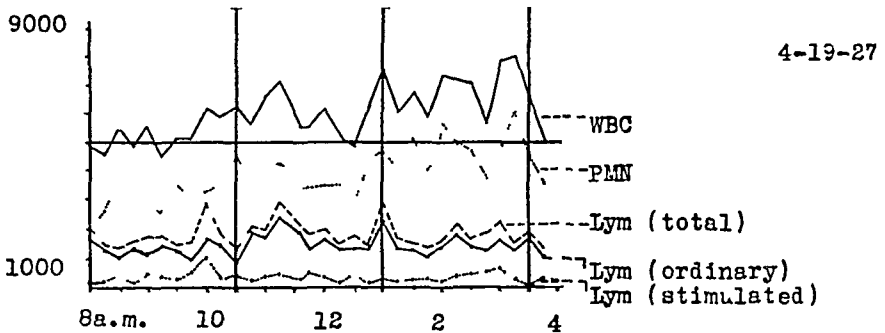
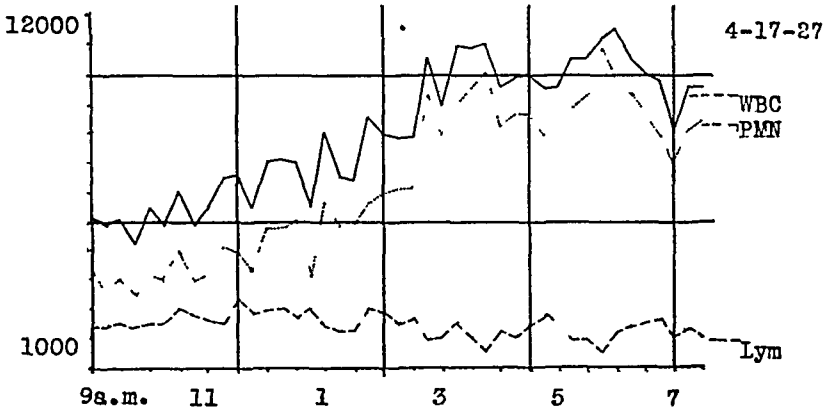
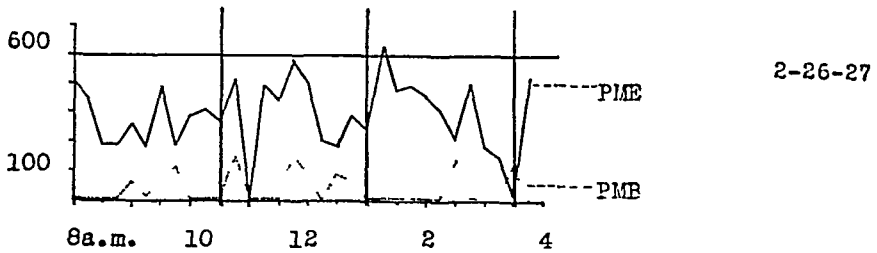


Chart 2—The exact curves of total and differential counts of subject B. Curve 5-2-27 represents a day's count during an intermenstrual period, and curves 2-26-27, 4-17-27 and 4-19-27 are counts taken during menstruation. Curve 4-17-27 is peculiar in that the subject had an attack of gastro-enteritis while the counts were being made.

cause Counts on both subjects, under somewhat different conditions six months later, exhibited the same individual patterns. Another consequence of this wider range in the counts of subject A is that the afternoon rise is much more pronounced than in the case of subject B. Individual differences in numbers of blood cells were noted by Rous (1908)<sup>23</sup> in a discussion of the quantities of lymphocytes supplied to the blood of the dog. He said that "the tissues producing the lymphocytes are "set" at a rate of activity definite in the individual."<sup>24</sup> Shaw<sup>2</sup> found that in human blood "the total number of leukocytes is influenced by the personal factor."<sup>25</sup> On the whole, the curves of subject A are slightly more irregular during menstruation (curves 3-2-27, 3-3-27, 3-4-27, 3-29-27, 3-30-27, 3-31-27, 4-25-27, 4-26-27, 4-27-27, charts 3 and

*High and Low Counts of White Blood Cells*

Subject A			Subject B		
Counts		Range of Count	Counts		Range of Count
Normal	4-10-27	5075-10775	Normal	5- 1-27	4800- 9382
Normal	4-11-27	5700-12075	Normal	5- 2-27	4590- 8570
Menstruation	3- 2-27	6933-10917	Menstruation	2-24-27	5266- 8800
Menstruation	3- 3-27	6390-12500	Menstruation	2-25-27	5600- 8932
Menstruation	3- 4-27	5375-11657	Menstruation	2-26-27	6182- 9666
Menstruation	3-29-27	9350-13425	Menstruation	3-23-27	5475-10425
Menstruation	3-30-27	6350-11044	Menstruation	3-24-27	5500- 8575
Menstruation	3-31-27	5424-11200	Menstruation	3-25-27	4625-10275
Menstruation	4-25-27	5050-12950	Day before menstruation	4-16-27	5390- 7505
Menstruation	4-26-27	5450-11200	Food poisoning	4-17-27	4200-11550
Menstruation	4-27-27	5175-11400	Menstruation		
Menstruation	5-22-27	6350- 9475	Menstruation	4-18-27	5125- 8825
No food			Menstruation	4-19-27	4525- 9125
			Menstruation	5-15-27	5150-13775
			No food		
			Menstruation	5-16-27	5075- 8875
			No food		
			Menstruation	5-17-27	4025- 8500
			No food		

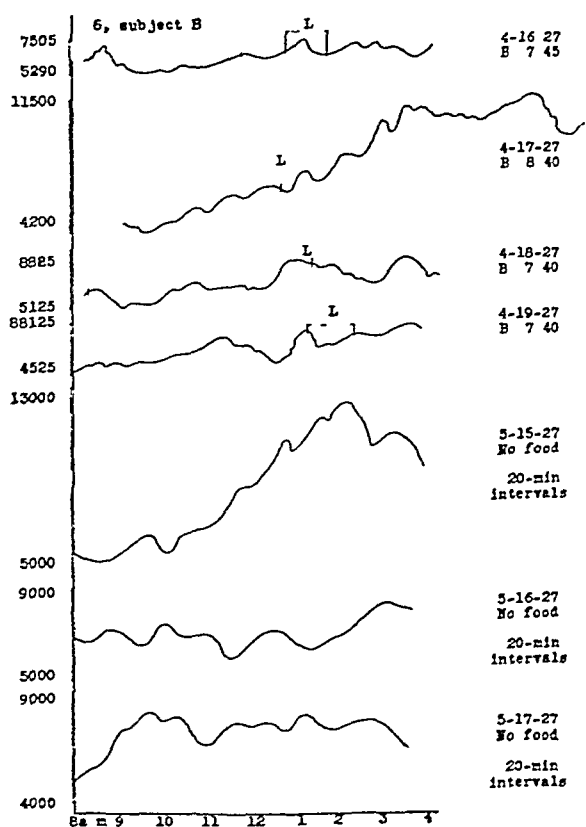
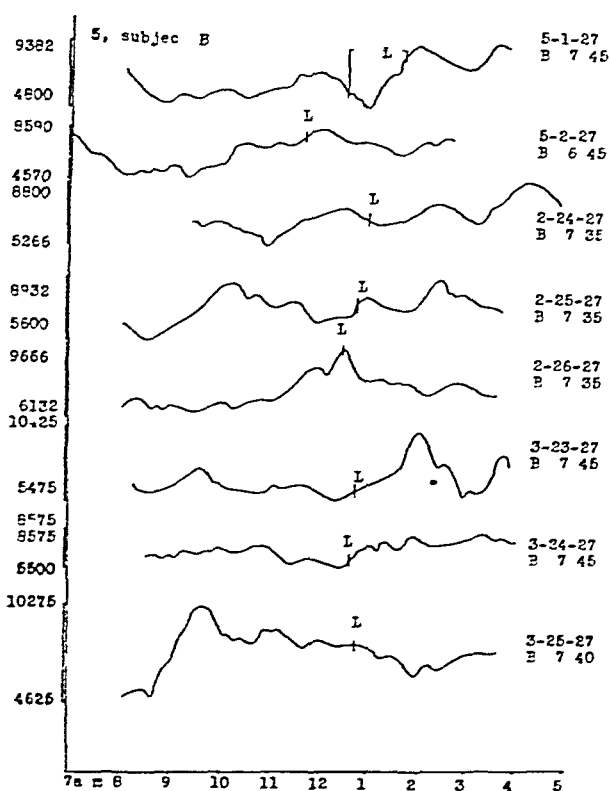
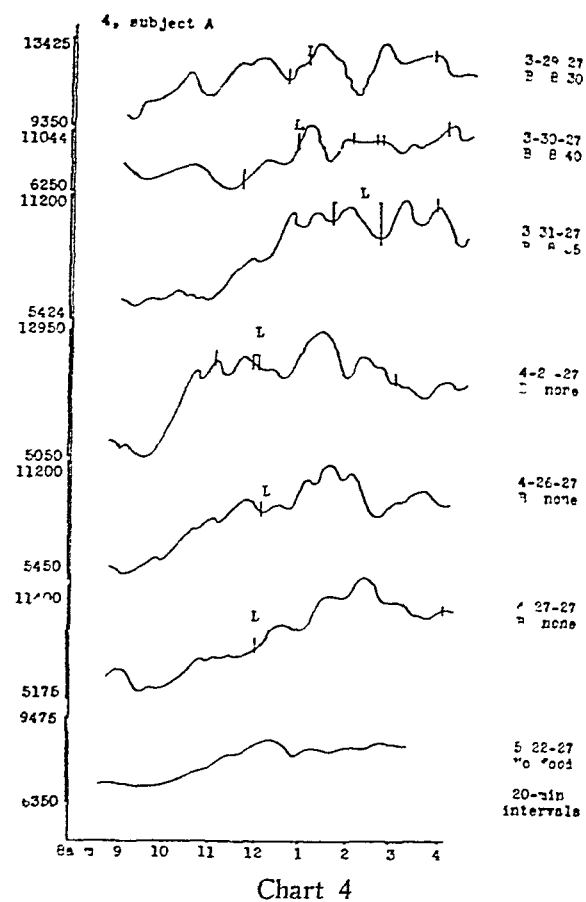
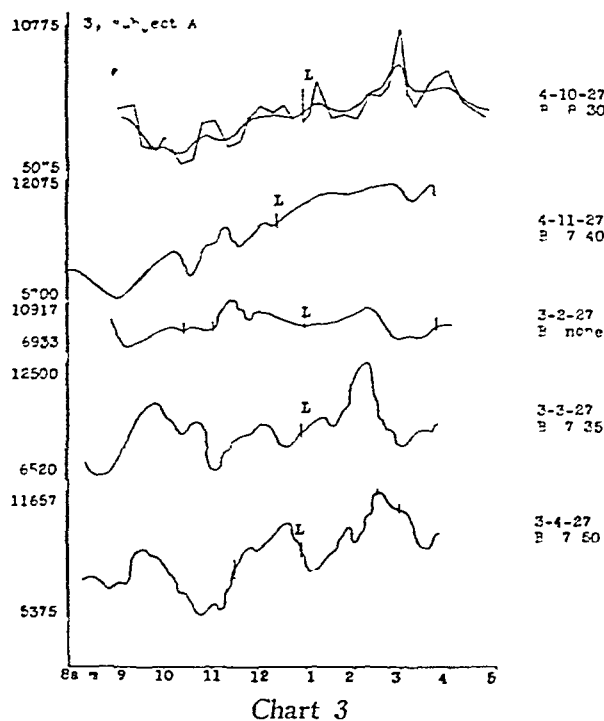
4) than are the normal curves (4-10-27 and 4-11-27, chart 3) as described in another paragraph. Such an effect is not apparent in the curves of subject B (charts 5 and 6).

Menstruation does not have a decided influence on the numbers or rhythm of the white blood cells. As already noted, the counts for this part of the work were made during the first three days of menstruation. The number of the cells is perhaps slightly increased, as seen in the accompanying table. The lower level of the menstrual counts is higher than the lower level of the normal counts, with the exception of 4-25-27 and 5-17-27. Three times in the case of subject A (3-3-27, 3-29-27, 4-25-27) and four times in the case of subject B (2-26-27, 3-23-27, 3-25-27, 5-15-27) the highest point of the menstrual counts is above the

<sup>23</sup> Rous, F. P. J. Exper. Med. **10** 238, 1908.

<sup>24</sup> Rous (footnote 23, p. 268).

<sup>25</sup> Shaw (footnote 2, p. 19).



Charts 3, 4, 5 and 6—These charts show general curves of total white counts which are representations of the exact curves. Curve 4-10-27 shows an exact curve superimposed on its flattened curve. These flattened curves are used to show the larger fluctuations and general tendencies.

highest point of the normal counts. However, this difference is so slight and inconstant that a definite conclusion cannot be made.

The menstrual curves of subject A present larger fluctuations than the normal curves. The normal curves (4-10-27, 4-11-27, chart 3, 4-11-27, chart 1) are more even, the afternoon rise follows the mean level fairly regularly and is not indented by deep depressions, except from 3 to 4 o'clock. On the contrary, the afternoon counts of the menstrual curves (3-2-27, 3-3-27, 3-4-27, chart 3) alternate fairly rapidly between high points and low points, the latter being almost as low as the low points of the morning counts. The morning counts of normal and menstrual curves are similar.

**Afternoon Leukocytosis.** Digestion apparently is not the cause of the afternoon leukocytosis. A study of the curves shows that breakfast does not influence the white blood cell picture, since a constant difference is not noticed between the curves for the days when breakfast was eaten and those for the days when breakfast was omitted. That lunch likewise is not a constant factor is seen by the fact that the highest point of the afternoon rise may come at any time and does not bear any relation to the time of eating lunch (charts 2, 4, 5 and 6). The small quantities of food eaten irregularly do not have a marked effect, since on some days no food except breakfast and lunch was eaten, yet the respective curves do not present constant variations due to this factor.

That the afternoon rise is not due to digestion is conclusively shown by a day's count made on subject A (curve 5-22-27, charts 1 and 4), when she ate nothing from dinner the night before (except an orange at midnight) till the end of the count, and by two days' counts made on subject B, when she ate nothing between dinner the night before and the end of the count. A third day's count made under similar conditions on subject B showed a morning rise (curve 5-17-27, previously referred to). Curve 5-22-27 (subject A, chart 1) is representative of these counts, with due allowance for the lower numbers of cells in the case of subject B. It shows quite as marked an afternoon rise as do the curves of days when food was not eaten.

A condition of fatigue apparently does not have a constant influence on the white blood cell count. From five to six hours was the amount of sleep taken the nights before the counts shown in curves 3-23-27, 3-24-27, 3-25-27 (chart 5) and 4-18-27 (chart 6). While curve 3-25-27 is the reverse of the typical curve, in having its high points in the morning, the other counts made under similar conditions do not show this characteristic, again, the counts shown on another reverse curve (3-2-27, chart 3) were made on a day following the normal amount of sleep (between seven and eight hours).

Physiologic response to a digestive disturbance has a marked effect on the numbers of the white blood cells, although the hourly rhythm

is maintained, this is in contrast to the slight or negative influence of normal physiologic processes (menstruation, digestion) Curve 4-17-27 (charts 2 and 6) shows the increase in numbers due to an attack of gastro-enteritis, the symptoms of which lasted from 12 to 4 o'clock

Observations on the Differential Counts 1 Neutrophils The observations of Sabin, Cunningham, Doan and Kindwall<sup>1</sup> and of Shaw<sup>2</sup> that the curve of the neutrophils follows that of the total white cells is confirmed in this study

The observations already recorded concerning the influence of physiologic factors (menstruation, digestion and fatigue) on the total number of white cells hold true specifically for the neutrophilic rhythm, that is, (1) menstruation possibly causes a slight increase in numbers in both cases, and greater irregularity in rhythm in the case of subject A, (2) digestion does not have a constant effect on the numbers or rhythm of the cells, and (3) fatigue does not have a constant effect on the numbers or rhythm of the cells

In contrast to the observations of Sabin, Cunningham, Doan and Kindwall<sup>1</sup> the nonmotile neutrophils, as already discussed under "Types of White Blood Cells," were not found in sufficiently large numbers to influence the neutrophilic, and therefore indirectly, the total white curve (curve 4-11-27, chart 1)

2 Basophils and Eosinophils These cells occur in small numbers (basophils, from 0 to 2 per cent and eosinophils, from 0 to 5 per cent) and are frequently absent in counts of a hundred cells There seems to be no regularity in the variations of their numbers (curve 2-26-27, chart 2)

3 Lymphocytes As noted by Sabin, Cunningham, Doan and Kindwall,<sup>1</sup> the numbers of the lymphocytes oscillate in a half hourly rhythm, but there is no constant rise in the mean level correlated with the time of day (curves 3-31-27, 4-11-27, chart 1, 4-17-27, 4-19-27, 5-2-27, chart 2) Menstruation, digestion and fatigue do not have any effect on their numbers or their rhythm The stimulated and ordinary types of lymphocytes are plotted separately on curve 4-19-27 (chart 2) From this it is seen that the curve for the ordinary lymphocytes closely follows the total curve, much as the neutrophilic curve follows the total white curve The stimulated lymphocytes, being fewer in number, do not influence the total lymphocyte curve so greatly The ratio of stimulated to ordinary lymphocytes is practically the same on all curves and therefore is not influenced by different physiologic conditions There was also no correlation between the numbers of stimulated lymphocytes and the time which elapsed between the making of the slide and the actual count Therefore they are not expressions of degenerative changes, but rather seem, as Maximow<sup>10</sup> said, to represent a greater degree of functional

activity of the cell Curves 3-31-27 (chart 1) and 5-2-27 (chart 2) show the correlation of fixed and vital lymphocyte counts

4 Monocytes The observations of Sabin, Cunningham, Doan and Kindwall<sup>1</sup> that the monocytes tend to have an hourly rhythm similar to the rhythm of the neutrophils have been confirmed Variations do not occur in connection with the time of day or with different physiologic factors Curve 5-2-27 (chart 2) shows the correlation of fixed and vital monocyte counts

*Comment and Review of Literature*—As Sabin, Cunningham, Doan and Kindwall<sup>1</sup> have pointed out, much of the previous work on the determination of the normal number of blood cells has been to find the average number rather than the normal range in numbers for an individual Doan and Zerfas<sup>26</sup> (1927) emphasized the necessity of the "zonal concept" in blood counts and, according to the experiments recorded in this paper, this point of view is valid

From the data obtained in this work, we believe that there is not only a zone of variation for each person but a characteristic pattern as well Although no two curves are identical and although curves for consecutive days are no more alike than curves for days a week or a month apart, curves for each person possess a similarity which can be seen readily The wider range or zone of one individual results in a curve with marked acute depressions and peaks, whereas the narrower range of the other makes for a more even curve This pattern concept is upheld by comparison of counts made six months apart on the same two subjects The striking conformity of the later curves to the pattern of those given in this paper is more than a coincidence

These studies also confirm the observations of those workers who believe that there is a characteristic rhythm of the white blood cells, both total and differential, and that the increase in the afternoon is not dependent on food intake Although these experiments were not primarily undertaken to investigate digestive leukocytosis, some points may be noted which have a bearing on the subject The numbers, rhythm and afternoon rise of the various types do not differ fundamentally on the days when food was not eaten, on the days when only breakfast and lunch were eaten, and on the days when small amounts were eaten irregularly in addition to breakfast and lunch There is also no definite correlation between the mealtimes and the afternoon leukocytosis

While it cannot be said absolutely that digestion may not have some effect on the numbers of the white blood cells, the conclusion is obvious that it does not have such a profound effect as has been thought Whatever slight effects it may have in these counts cannot be determined since too many other factors are involved The rhythmic variations in

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26 Doan, C. A., and Zerfas, L. G. J. Exper. Med. **46** 511, 1926

the numbers of the white blood cells must then have some other underlying cause than digestion Japha<sup>27</sup> (1900) was one of the first to record variations in the blood count regardless of digestion Sabin, Cunningham, Doan and Kindwall<sup>1</sup> and Shaw<sup>2</sup> found that variations in the white count occur whether food is eaten or not Sabin, Cunningham, Doan and Kindwall further found that these changes occur in an almost hourly rhythm during the day, with a total increase in the afternoon, and that the numbers of the different kinds of cells also vary in a typical rhythm However, the majority of authors still believe that digestion causes a rise in the number of the white blood cells, as seen in the reviews of the literature given by Mitchell<sup>28</sup> (1915), Sabin, Cunningham, Doan and Kindwall,<sup>1</sup> Plichtet<sup>29</sup> (1927) and Shaw<sup>2</sup>

Another important physiologic factor to be taken into consideration when making experiments on women is menstruation As has been previously noted, Novak and Te Linde<sup>3</sup> described a lymphocytic and a leukocytic infiltration of the endometrium just preceding the onset of menstruation A statement is not made about the presence of white cells in the uterine wall on the first day of the menstrual period, but on the second the infiltration is said to be less than that of the early stages At this time lymphocytes are the predominant cells Although such an infiltration may occur, it does not seem to be of sufficient magnitude to disturb the number of cells (unless it causes a slight increase) or their percentage in the peripheral blood The curves for counts made during menstruation differ from each other as much as they do from curves for the days during intermenstrual periods

It is current opinion that the greatest changes in the metabolism of women occur within the few hours preceding or immediately after the beginning of menstruation Counts were made during seven cycles, but only two were made within the first hours after the onset Curve 3-29-27 (chart 4) for subject A is of a count which was started one and one-half hours after the beginning of the period but there is no difference in the form of the curve The curve for subject B does not offer evidence in regard to this point, as it is the one which also shows the results of gastro-enteritis All of the other counts were made several hours after the start of the menstrual flow In their work on the studies of metabolism of women, Okey and her associates (1925, 1926 and 1927)<sup>30</sup>

27 Japha, A *Jahrb f Kinderh* 52 242, 1900

28 Mitchell, A G *Leukocyte Counts During Digestion of Bottle-Fed Infants* *Am J Dis Child* 9 358 (May) 1915

29 Plichtet, A *Le sang biol et path* 1 134, 1927

30 Okey, R, and Robb, E I *J Biol Chem* 65 165, 1925 Okey, R, and Erikson, S E *Ibid* 68 687, 1926 Okey, R, and Boyden, R E *Ibid* 72 261 1927

found the same difficulty. They were able to make determinations during the first few hours of menstrual bleeding in only a small percentage of cases.

Although in subject A the curves are slightly more irregular during menstruation, such an effect is not seen in the curves of subject B. Okey and Robb,<sup>31</sup> in their work on the blood sugar level during fasting noticed a greater deviation from the average during the menstrual period, although they did not find a consistent cyclic variation. Greisheimer<sup>32</sup> (1927) observed that the blood sedimentation rate of women is faster than in men but that it is not faster during periods than between periods.

It has been shown that there is some evidence for cyclic variations in the metabolism of women by studies on measured activities and on the chemistry of the blood. Moore and Barker<sup>33</sup> (1923) and Moore and Cooper<sup>34</sup> (1923) demonstrated low menstrual and high intermenstrual variations in muscular efficiency, in cardiovascular changes and in respiratory rate. Okey and Erikson<sup>35</sup> and Okey and Boyden<sup>36</sup> observed low menstrual values for blood uric acid and cholesterol. Total non-protein nitrogen was found to be high during or just after the period. The fatty acid tended to vary, but the determinations of lecithin were more nearly constant. Although from this brief summary it is seen that some of the constituents of the blood may exhibit certain cyclic changes in relation to menstruation, neither they nor the leukocytic infiltration of the uterine wall at that time produces any marked modification in the white blood cell picture.

Variations in the numbers of white blood cells have been ascribed to various physiologic factors. In this study, the slight or negative influence of digestion, menstruation and moderate fatigue bring out the fact that the rhythm of the white blood cells tends to be constant in different persons and to conform to characteristic patterns. It is thought that this rhythm is really a functional activity of the cells themselves, and cannot be explained as being caused, although it may be influenced, by extrinsic physiologic factors, just as the heart beat is not caused but may be modified by external factors.

Regarding the rhythms of the different kinds of white blood cells, it is apparent from the curves (charts 1 and 2) that the rhythm of the whole number of the white cells is determined by the rhythm of the neutrophils, this is to be expected, since they form the greater proportion of the white cells. The question, then, concerning the cause of the gen-

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31 Okey and Robb (footnote 30, first reference)

32 Greisheimer, E. M. *Am J M Sc* **174** 338, 1927

33 Moore, L. M., and Barker, J. L. *Am J Physiol* **64** 405, 1923

34 Moore, L. M., and Cooper, C. R. *Am J Physiol* **64** 416, 1923

35 Okey and Erikson (footnote 30, second reference)

36 Okey and Boyden (footnote 30, third reference)



elial rhythm of the white cells narrows itself down to the cause of the rhythm of the neutrophils. This study does not confirm the belief of Sabin, Cunningham, Doan and Kindwall<sup>1</sup> that the neutrophils die out in the circulation in fairly large numbers, since the observations indicate that the dead nonmotile cell, although sometimes appearing as a dying neutrophil in the blood stream, is more often an artefact due to technic in the supravital smears. Neither is there any explanation for the half hourly rhythm of the lymphocytes, the hourly rhythm of the monocytes, the irregular rhythm of the basophils and eosinophils or the constant mean numbers of all four groups. It can only be said that the numbers of white blood cells in the peripheral circulation are maintained within certain limits and fluctuate regularly within these limits. This occurrence may be an expression of the fundamental rhythmicity of vital activities which Rogers<sup>37</sup> (1927) defined as "the tendency of the fundamental or even incidental operations of the cells of the animal body or of the organism to alternate or oscillate from one side to the other of certain mean values."

#### CONCLUSIONS

1 Evidence indicates that the small basophil may be an intermediate stage in the development of certain eosinophils of lymphocytic origin.

2 The characteristics of the normal rhythm of the white blood cells previously described have been confirmed in general, except that it is not believed that cells die in the peripheral circulation to such an extent that the neutrophilic curve is influenced by them.

3 The number of white blood cells varies within certain limits. These limits are different in different persons, under normal conditions, they are constant in a given person.

4 The curves representing the daily rhythm of the white blood cells have a characteristic pattern for each person.

5 The number and rhythm are essential characteristics of the white blood cell picture and are not caused or fundamentally modified by normal physiologic processes (digestion, menstruation) or different physiologic states of the normal body (mild fatigue, moderate exercise).

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<sup>37</sup> Rogers, C. G. *Text-Book of Comparative Physiology*, New York, McGraw and Hill, 1927, p. 69.

# FATAL PHENOBARBITAL POISONING

## REPORT OF A CASE WITH TOXICOLOGIC ANALYSIS

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Although it is now fifteen years since its introduction into therapeutics, there does not appear to have been a case of fatal poisoning definitely attributable to phenobarbital so far recorded in the literature, despite the fact that it is undoubtedly the most widely used sedative and anticonvulsant drug

A number of reports of toxic reactions and skin eruptions following the use of phenobarbital have appeared, but only one of these cases proved fatal, and this does not seem to have been attributable to the drug

In 1926, Hamilton, Geiger and Roth<sup>1</sup> reviewed the literature on phenobarbital poisoning, and found only six cases reported previous to their own—two by Haug,<sup>2</sup> two by Farnell<sup>3</sup> and one each by Stein<sup>4</sup> and Hueber<sup>5</sup>. All of the patients recovered except that of Hueber, whose death was probably due to a flaring up of an old tuberculous condition. Toxic reactions other than those cited by Hamilton et al, however, were reported by Ungar,<sup>6</sup> Nicolai,<sup>7</sup> Weig<sup>8</sup> and Carlill<sup>9</sup>.

Still more recently, Jackson<sup>10</sup> reported six cases of acute phenobarbital poisoning, in all of which recovery occurred. There are also reports by Stone<sup>11</sup> of a case of phenobarbital poisoning simulating mul-

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\* Submitted for publication, Aug 27, 1928

\* From the Department of Pharmacology, University of Minnesota

1 Hamilton, E S, Geiger, C W, and Roth, J H Luminal Poisoning with Conjunctival Residue, Illinois M J **49** 344 (April) 1926

2 Haug, W Zwei Falle von Luminalvergiftung, Munchen med Wchnschr **66** 1494, 1919

3 Farnell, F J Luminal, Its Toxic Effects, J A M A **61** 192 (July 19) 1913

4 Stein, J Case of Luminal Poisoning, Therap Halbmonatsh **34** 387 (July 15) 1920

5 Hueber, D Ein Fall von Luminalvergiftung mit todlichem Ausgang, Munchen med Wchnschr **66** 1090, 1919

6 Ungar, T Ein Fall von Luminalvergiftung, Wien klin Wchnsch **27** 847, 1914

7 Nicolai, H W Phenobarbital Poisoning, Klin Wchnschr **2** 1891 (Oct 8) 1923

8 Weig, F L Zur Luminalvergiftung, Deutsche med Wchnschr **51** 272, 1925

9 Carlill, H Luminal Poisoning, Lancet **2** 596 (Sept 19) 1925

10 Jackson, A S Toxic Reaction from Phenobarbital, J A M A **88** 642 (Feb 26) 1927

11 Stone, C W Barbitol Poisoning Simulating Multiple Sclerosis, Ohio State M J **23** 132 (Feb) 1927

tiple sclerosis and of two toxic reactions by Bollinger<sup>12</sup> Menninger<sup>13</sup> reported three cases of skin eruptions which occurred among 400 patients

The distribution of phenobarbital in the tissues does not seem to have been studied, but would presumably follow closely the distribution of the other barbituric acid derivatives. Fabre and Fredet<sup>14</sup> studied the distribution of barbital and allyl-isopropyl barbituric acid in dogs killed shortly after the ingestion of a hypnotic dose of the barbituric acid derivatives. These observers found the drug to be largely concentrated in the brain, with smaller quantities in the spleen, kidney and liver.

The question of the excretion of the barbituric acid derivatives in the urine has not at present been satisfactorily settled. In fourteen patients receiving barbital in amounts of from 0.5 to 2 Gm, Reiche<sup>15</sup> recovered from 0.18 to 11.7 per cent of the amount ingested from the urine in thirty-eight hours.

*Amount of Phenobarbital and Allyl-Isopropyl Barbituric Acid Recovered  
from One Hundred Grams of the Organ*

	Barbital	Allyl isopropyl Barbituric Acid
Brain	138 mg	68 mg
Spleen	44 mg	32 mg
Kidney	5 mg	5 mg
Liver	4 mg	6 mg

Luce and Feigl<sup>16</sup> and, later, Fleury and Guinnebault<sup>17</sup> determined the elimination of phenobarbital in dogs under continuous administration of from 0.2 to 0.3 Gm daily but observed only the excretion of small quantities. Halberkann and Reiche<sup>18</sup> reported that after they gave 1.8 Gm of phenobarbital to a series of patients, they recovered from 11 to 25 per cent of the ingested drug over a period of eight days.

12 Bollinger, H. J. Toxic Reactions from Phenobarbital, Two Cases, California & West Med **26** 659 (May) 1927

13 Menninger, W. C. Skin Eruptions with Phenobarbital, J. A. M. A **91** 14 (July 7) 1928

14 Fabre, R., and Fredet, P. Studies in the Localization and Elimination of Some Derivatives of Malonyl Urea, J. de pharm. et de chim **2** 321, 1923

15 Reiche, F. Zur Kenntnis der Veronalvergiftung und der Veronalausscheidung, Klin. Wchnschr **5** 2112 (Nov. 5) 1926

16 Luce, H., and Feigl, J. Ueber Luminal-Erythema, Therap. Monatschr **32** 236, 1918

17 Fleury, P., and Guinnebault, E. L'élimination de la phenylethylmalonyluree, Comp. rend. Soc. de biol. **93** 1508, 1925

18 Halberkann, J., and Reiche, F. Ueber die Ausscheidung einiger viel verwendeter Barbitalsäureverbindungen mit dem Urin, München med. Wchnschr **74** 1450, 1927

Reinert<sup>19</sup> obtained about 20 per cent excretion over a period of ten days in dogs fed 1.5 Gm of phenobarbital. The greatest excretion occurred during the third and fourth days. Wetselaar<sup>20</sup> reported that phenobarbital is not found in the urine in cases of acute poisoning.

#### REPORT OF CASE

L. C., a woman, aged about 35, was found dead in a room of a Minneapolis hotel. She had apparently been dead about twenty hours when found. Evidence of poison was not found in the room, but it was known that the woman had been in the habit of taking phenobarbital. The autopsy did not show anything significant. The stomach and its contents and portions of the liver, brain and about 50 cc of urine were removed for toxicologic analysis. The urine was extracted several times with 25 cc portions of ether, and the combined ether extracts evaporated to about 20 cc. This was then extracted with 5 cc of five hundredth-normal sodium hydroxide. A small portion of this alkaline extract, after acidification with acetic acid, gave a faint turbidity with lead acetate solution, which would indicate the probable presence of a trace of one of the barbituric acid derivatives, but there was not a sufficient amount present for identification. It would appear, then, that in the case of phenobarbital, the excretion of the drug in the urine is too slow to serve either as a diagnostic aid in cases showing toxic reactions, as is possible with barbital poisoning (Leake and Ware<sup>21</sup>), or as a source of identification of the drug in the toxicologic analysis of fatal poisoning.

The stomach and liver were hashed separately, and extracted repeatedly with sufficient ether to cover the material. The combined ether extracts were filtered and evaporated to a volume of 40 cc and extracted twice with 10 cc of five hundredth-normal sodium hydroxide. Considerable care has to be exercised in making this extraction with alkali, as the mixture shows a marked tendency to emulsify, and if shaken violently, the whole mass becomes almost solid and the emulsion can be broken only by complete evaporation of both solvents.

The aqueous extract thus obtained still contained considerable impurities, chiefly split proteins and soaps which are soluble in alkaline solution.

The process of purification was continued, therefore, by acidifying the aqueous extract with 50 per cent acetic acid and extracting the slightly acid liquid several times with ether, most of the proteins and soaps being left in the water layer. The ether extracts, after filtration and concentration, were extracted with dilute alkali. As judged by the reaction of a few drops of this solution, after acidification with acetic acid to a solution of lead acetate, which precipitates both the barbituric acid derivative and the dissolved proteins, the amount of impurity present was now slight.

The alkaline solution was now made slightly acid with acetic acid. In the case of the extract from the liver, there was just sufficient phenobarbital present to exceed the solubility of this drug in water (1 mg per cubic centimeter) and to give a faint turbidity to the solution, while the extract obtained from the stomach was not sufficiently concentrated to do this.

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19 Reinert, M. Ueber die Ausscheidung von Barbitursäurederivaten im Harn beim Hund, *Arch f exper Path u Pharmacol* **130** 49, 1928.

20 Wetselaar, D. Y. K. *Pharm Weekblad* **59** 521, 1922.

21 Leake, W. H., and Ware, E. R. Barbital Poisoning, *J. A. M. A.* **84** 434 (Feb. 7) 1925.

In order to recover as much phenobarbital as possible, as crystallization from water did not appear feasible, the acid aqueous extracts were extracted several times with ether and the ether allowed to evaporate spontaneously. The residue obtained was a white powder, having a melting point of 170 C. Phenobarbital melts between 172 and 174 C<sup>22</sup>. The identity of the material obtained by extraction was established as phenobarbital by taking a mixed melting point of a 50-50 mixture of the residue and a known sample of phenobarbital (melting point, 172 C). The melting point so obtained was 170.5 C. If the two substances had not been identical chemically, the melting point of the mixture would have been considerably depressed.

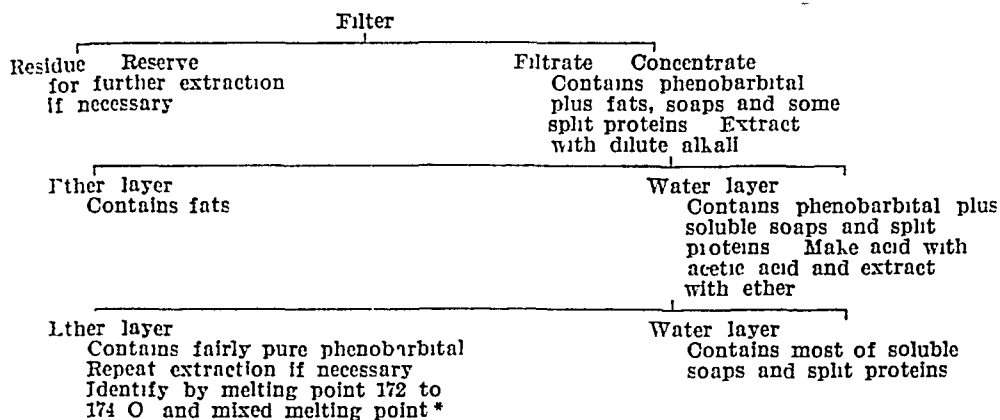
The amount of phenobarbital obtained from the stomach was from 5 to 6 mg and from the liver from 15 to 20 mg.

Extraction of the phenobarbital from the brain presented somewhat more difficulty on account of the presence of large quantities of lipoids and fats, although the phenobarbital content of this tissue should be considerably higher. Portions of the brain were hashed and extracted for several days with ether. The ether extract was then removed and filtered, and the ether allowed to evaporate. The residue was taken up in 2 cc of ether and poured into 50 cc of alcohol and filtered. This removes most of the fats and the cephalin. The alcohol was then removed by evaporation on the water bath (or by distillation) and the residue taken up in acetone, in which the lecithin is insoluble. After filtration, the acetone was removed by evaporation and the residue taken up in a small quantity of boiling water and filtered. After the mixture was cooled in the icebox, a white precipitate was obtained, which, after recrystallization, melted at 170 C, and the melting point was not depressed by mixing with known phenobarbital.

The approximate amounts of phenobarbital isolated from the various organs per hundred grams was: stomach, from 3 to 4 Gm; liver, 5 Gm and brain, 90 mg.

The following schema would appear to be a satisfactory method for the toxicologic analysis of poisoning by phenobarbital.

Hash tissue and extract from three to five times with ether.



\* If any difficulty is experienced in removing soaps, which may be carried over into the ether layer on extraction in acid solution, they may be readily removed by treating the acid aqueous solution with a slight excess of barium chloride solution and filtering off the precipitated barium soaps.

## SUMMARY

- 1 A case of fatal poisoning from phenobarbital is reported
- 2 A method is presented for the toxicologic analysis of phenobarbital, including extraction and identification from the stomach, liver and brain
- 3 Phenobarbital does not appear to be excreted in the urine in cases of acute poisoning

# MUSTARD GAS AND TUBERCULOSIS

## AN EXPERIMENTAL STUDY <sup>1</sup>

AMOS R KOONTZ, M D

BALTIMORE

Since the introduction of toxic gases into modern warfare on April 22, 1915, all sorts of dire late sequelae have been declared the result of exposure to the various war gases. Peribronchial thickenings and scarring of the parenchyma of the lung have been much discussed, various functional disturbances have been attributed to the late effect of gassing. As a result of several years of experimental work, I <sup>1</sup> published data in 1925 which showed that there was little or no pathologic basis for the many symptoms attributed by the ex-soldier to the fact that he had been gassed during the war.

The question of a possible causal relationship between exposure to the various war gases and the development of pulmonary tuberculosis has agitated the minds of both the medical profession and the laity from the time of the earliest use of these gases. Both the medical profession and the laity believed at first that soldiers who had been gassed would be especially susceptible to pulmonary tuberculosis. Subsequent facts did not justify this fear. The belief, however, that there is a close causal relationship between gassing and tuberculosis has remained firmly fixed in the minds of the laity and also in the minds of those physicians who have not kept abreast of the times by studying the current medical literature. The literature on the clinical aspects of this subject was recently reviewed by me <sup>2</sup>. The question has been discussed by the medical profession, and, on the basis of clinical observations, physicians are gradually becoming convinced that the belief was not justified. A large number of physicians, working with ex-soldiers who were gassed during the war, have amassed a considerable volume of clinical data. There is overwhelming evidence that gassing does not predispose to pulmonary tuberculosis.

### HISTORICAL

No matter how convincing clinical evidence relative to any mooted question may be, the wisdom of applying the test of experimentation

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<sup>1</sup> Submitted for publication, Aug 16, 1928

<sup>2</sup> From the Pathological Section, Medical Research Division, Chemical Warfare Service, Edgewood Arsenal, Edgewood, Md

1 Koontz, A R. When Do Lungs Return to Normal Following Exposure to War Gases? *Arch Int Med* **36** 204 (Aug) 1925

2 Koontz, A R. War Gases and Tuberculosis. An Experimental Study, *Arch Int Med* **39** 833 (June) 1927

cannot be questioned. The conditions determining the laws of cause and effect can be controlled and studied in experiments on animals in a manner quite impossible with human clinical material. For this reason, several years ago I<sup>2</sup> undertook a series of experiments in an effort to determine what relationship, if any, existed between exposure to high concentrations of toxic gases and the development of pulmonary tuberculosis. Large numbers of rabbits were given varying doses of tubercle bacilli in the vein of the ear, so that the first point of lodgment would be the capillary bed of the lungs. Half of the animals were gassed with mustard gas, phosgene and lewisite at varying times, before and after the injection of the tubercle bacilli, the other half were kept as controls. The experiments clearly demonstrated that the gassed rabbits were not more susceptible to tuberculosis than were the control animals inoculated at the same time with the same dose of bacilli. Indeed, the number of lobes of the lung involved in the gassed animals was slightly less than in the controls. It was further shown that the gassing of animals that already had well developed tuberculosis did not appreciably accelerate the progress of the tuberculous process.

It was noted in these experiments that the difference between the amount of tuberculosis in the animals gassed with lewisite and in the controls was greater than that between the animals gassed with mustard gas and phosgene and their controls. The reason for this fact was believed to be that the animals gassed with lewisite received much smaller doses of tubercle bacilli than those gassed with mustard gas and phosgene, it was easier to detect differences because the infection was not so generalized and not so massive as when larger doses of bacilli were injected. I was, therefore, led to believe that had smaller doses been used throughout the experiments, the results might have shown an even greater difference between the amount of tuberculosis in the gassed animals and in the controls. The results of the experiments with lewisite pointed to an actual inhibiting effect of this gas on the development of pulmonary tuberculosis. They made me wonder whether these impressions would be confirmed by a larger number of experiments, and also whether the same inhibitory influence could be shown to be possessed by the other important gases used in the war.

#### EXPERIMENTAL WORK

It was determined, therefore, to conduct a more extensive series of experiments, as opportunity presented, dealing separately with each of the principal war gases and using small doses of bacilli in order to determine just what inhibitory effect, if any, they might prove to have on the development of pulmonary tuberculosis.

Mustard gas was the first gas investigated, and the series of experiments conducted with this gas have now been completed. My purpose in this paper is to present the results obtained



## METHOD

In each set of experiments, all animals were inoculated with the same dose of tubercle bacilli per kilogram of body weight. Half of the animals were kept as controls, while the other half were gassed with approximately the lethal concentration of mustard gas. All animals, both controls and gassed animals, were killed from six to ten weeks after inoculation. A notation was made as to the number of cases of tuberculosis in both gassed animals and controls. Each animal having tuberculosis was marked one plus, two plus, three plus or four plus, according to the number of lobes of the lung involved. (The two upper lobes of the right lung were considered as one lobe.) The presence or absence of tuberculosis was determined by both gross and microscopic examination.

Young glycerin-broth cultures of virulent human tubercle bacilli were used in all experiments. Although the cultures used were from the same strain as those used in the experiments reported previously,<sup>2</sup> it was noted that the virulence of the strain had become considerably attenuated, and that larger doses than before were necessary to produce the same amount of tuberculosis.

All rabbits were weighed at the time of inoculation and at autopsy, as in the previous experiments.<sup>2</sup> This has served only to confirm my original conclusions that this information is valueless. Rabbits with tuberculosis gain weight steadily, while others without tuberculosis and kept under exactly the same living conditions, may lose weight, for no accountable reason. The data, therefore, with regard to weight have been left out of the tables.

## COMMENT

The results of some of the experiments are shown in the tables, lack of space has prevented the tabulation of all experiments. Tables 1 to 3, inclusive, show in detail the results of typical experiments. Table 4 tabulates the results obtained from all experiments and shows the total number of gassed animals and controls that developed tuberculosis, it also shows the extent of the tuberculous process in the tuberculous animals, as indicated by the number of lobes of the lung involved. Animals that died in less than ten days from the date of inoculation with tubercle bacilli, from the effects of gassing or other causes, are not included in this total, since these animals could not possibly have developed tuberculosis so soon after inoculation. This arbitrary time limit was applied to both the gassed animals and the controls, so as to include only those animals that really had an opportunity to develop tuberculosis. The inclusion of animals that died two or three days after inoculation from irrelevant causes would only have vitiated the results.

In only exceptional instances in this series of experiments was tuberculosis found in organs other than the lungs. This was undoubtedly due to the fact that only small doses of tubercle bacilli were injected, and that the strain had become somewhat attenuated since the experiments first reported<sup>2</sup> were conducted. On account of the small number of cases in which other organs than the lungs were involved, it is not considered worth while to include them in the tables as this would necessitate carrying a practically blank column.

That gassing with mustard gas has an inhibitory effect on the development of pulmonary tuberculosis is clearly shown by a study of these tables. Only 64 per cent of the total number of gassed animals developed tuberculosis, of the total number of controls which were inoculated at the same time with the same dose of bacilli, 83 per cent developed the disease. In the gassed animals that developed tuberculosis, 42 per cent of the possible total number of lobes of the lung were involved, while in the controls that developed tuberculosis, 58 per cent of the possible total number of lobes were involved. Among all the animals that developed

TABLE 1—*Results Showing the Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

Number	Dose of Tubercle Bacilli* in Mg. per Kg. of Body Weight	Date Injected†	Result	Time Be- tween Injec- tion and Autopsy, Days	Time of Gassing in Relation to Injection	Lung Involve- ment
Gassed Animals						
425	0.005	11/30/26	Killed	46	2 weeks before and 20 hours after	- + + †
426	0.005	11/30/26	Died	18	2 weeks before and 20 hours after	-
427	0.005	11/30/26	Killed	46	2 weeks before and 20 hours after	- + + +
428	0.005	11/30/26	Killed	46	2 weeks before and 20 hours after	- + +
429	0.005	11/30/26	Killed	46	2 weeks before and 20 hours after	-
430	0.005	11/30/26	Killed	46	2 weeks before and 20 hours after	-
Controls						
431	0.005	11/30/26	Killed	46		- +
432	0.005	11/30/26	Killed	46		-
433	0.005	11/30/26	Killed	46		+ + + +
434	0.005	11/30/26	Killed	46		+ + + +
435	0.005	11/30/26	Killed	46		+ + + +
436	0.005	11/30/26	Killed	46		+ + + +

\* Twenty-two day old glycerum broth culture used for inoculations

† Twenty hours after inoculation, the first six animals in the table were gassed with mustard gas (concentration of 0.0152 mg. per liter of air) for one hour. These animals had also been gassed with mustard gas in a field test, two weeks previous to inoculation, concentration of gas and time of exposure unknown.

‡ The plus marks indicate the number of lobes involved.

tuberculosis, therefore, the extent of the tuberculous process was greater in the nongassed than in the gassed animals.

These results are in accord with the experience of Francine<sup>3</sup> who did not find an increase in tuberculosis in necropsies on soldiers who had been gassed. They are also in accord with the known clinical fact that tuberculosis is rare in persons who have mitral stenosis. Apparently, congestion of the lungs is a condition unfavorable to the growth of the tubercle bacillus. The congestion produced by mustard gas may be the factor responsible for its inhibitory effect on tuberculosis. This seems to me more probable than that there is a beneficial bactericidal action on

3 Gilchrist, H. L. Warfare Gas and Tuberculosis, Testimony of Dr. Albert P. Francine Before the Senate Committee, Mil. Surgeon 54 470 (April) 1924.

TABLE 2—Results Showing the Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed

Number	Dose of Tubercle Bacilli* in Mg per Kg of Body Weight	Date Injected†	Result	Time Be- tween Injec- tion and Autopsy, Days	Time of Gassing in Relation to Injection	Lung Involve- ment
Gassed Animals						
449	0.005	12/29/26	Killed	49	1 day before	—‡
450	0.005	12/29/26	Killed	49	1 day before	—
451	0.005	12/29/26	Killed	49	1 day before	—
452	0.005	12/29/26	Killed	49	1 day before	—
453	0.005	12/29/26	Killed	49	1 day before	—
454	0.005	12/29/26	Killed	49	1 day before	—
Controls						
455	0.005	12/29/26	Killed	49		++
456	0.005	12/29/26	Killed	49		++
457	0.005	12/29/26	Killed	49		++
458	0.005	12/29/26	Killed	49		++
459	0.005	12/29/26	Killed	49		—
460	0.005	12/29/26	Killed	49		++++

\* Seven day old glycerin broth culture used for inoculations

† One day before inoculation, the first six animals in the table were gassed with mustard gas (concentration of 0.0133 mg per liter of air) for one hour

‡ The plus marks indicate the number of lobes involved

TABLE 3—Results Showing the Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed

Number	Dose of Tubercle Bacilli* in Mg per Kg of Body Weight	Date Injected†	Result	Time Be- tween Injec- tion and Autopsy, Days	Time of Gassing in Relation to Injection	Lung Involve- ment
Gassed Animals						
509	0.01	4/11/27	Killed	51	1 day after	-----‡
510	0.01	4/11/27	Killed	51	1 day after	—
511	0.01	4/11/27	Killed	51	1 day after	-----
512	0.01	4/11/27	Killed	51	1 day after	—
513	0.01	4/11/27	Killed	51	1 day after	-----
514	0.01	4/11/27	Killed	51	1 day after	—
Controls						
515	0.01	4/11/27	Killed	51		-----
516	0.01	4/11/27	Died	22		-----
517	0.01	4/11/27	Killed	51		-----
518	0.01	4/11/27	Killed	51		-----
519	0.01	4/11/27	Killed	51		-----
520	0.01	4/11/27	Killed	51		—

\* Twelve day old glycerin broth culture, not growing very well, used for inoculations

† One day after inoculation, the first six animals in the table were gassed with mustard gas (concentration of 0.0174 mg per liter of air) for one hour

‡ The plus marks indicate the number of lobes involved

TABLE 4—Tabulation of Total Results from all Experiments

	Total Number of Animals	Number of Animals Developing Tuberculosis	Percentage of Animals Developing Tuberculosis	Total Number of Lung Lobes Involved	Percentage (of Possible Total) of Lung Lobes Involved
Gassed animals	73	50	64	130	42
Controls	77	64	83	178	58

the part of the gas Coiper and Rensch,<sup>4</sup> however, have reported that mustard gas is bactericidal for virulent human tubercle bacilli *in vitro*, and that when injected with bacilli into guinea-pigs, it distinctly retards the development of tuberculosis in these animals

#### SUMMARY AND CONCLUSIONS

One hundred and sixty-eight rabbits were inoculated in the vein of the ear with virulent human tubercle bacilli. Half of the animals were gassed for one hour with approximately the lethal dose of mustard gas, the other half were kept as controls. From six to ten weeks after their inoculation, all the animals were killed, autopsies performed, and the viscera studied for tuberculous lesions. Sixty-four per cent of the animals that had been gassed had pulmonary tuberculosis, 83 per cent of the controls had pulmonary tuberculosis. The tuberculous process was much more extensive in the control animals that developed the disease than in the gassed animals that contracted it.

These experiments clearly demonstrate that gassing with mustard gas has an inhibitory effect on the development of pulmonary tuberculosis in rabbits.

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<sup>4</sup> Corper, H. J., and Rensch, O. B. The Effect of Mustard Gas (Dichloroethylsulphide) on Experimental Tuberculosis, *J. Infect. Dis.* **28** 286 (March) 1921.

# NORMAL BLOOD DETERMINATIONS IN THE SOUTH \*

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NEW ORLEANS

The opinion has been frequently expressed that the red cell count and particularly hemoglobin are low in the South. Musser and Wirth<sup>1</sup> advanced the thesis that anemia is more prevalent in the South than the North. Lippincott<sup>2</sup> concluded that the normal average percentage of hemoglobin and erythrocyte counts in the region of the state of Mississippi are lower than the usually accepted standards. His determinations, however, were made on patients in hospitals and clinics, and his methods do not appear to have been accurate.

On the other hand, Major W P Chamberlain,<sup>3</sup> studying the blood of a large number of soldiers in the Philippines, found a normal count for red corpuscles and possibly a slightly lowered percentage of hemoglobin. Like Chamberlain, Balfour<sup>4</sup> expressed the belief that climate alone does not produce any change in the blood and that so-called tropical anemia is apparent rather than genuine.

In order to determine the accuracy of these statements, specimens of the blood of 100 healthy young men have been examined by the most accurate methods available. An excellent basis for comparison is furnished by the work of Osgood,<sup>5</sup> who reported red cell counts, hemoglobin and determination of cell volume on 137 young men living on the Western coast of the United States. In order to make comparison easier, our methods have been similar to those described by Osgood.

We have been further stimulated in our work by the need for a large series of accurate, normal examinations of the blood, made in different parts of the world, in order that accurate, normal figures on the blood may be computed. Few are aware that the figures at present accepted as normal are based on a small number of determinations carried out

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1 Musser, J H, and Wirth, Willard R. Anemia in the South, *Ann Clin Med* **5** 861 (March) 1927.

2 Lippincott, L S. Hemoglobin and Erythrocytes in the South, *J Lab & Clin Med* **12**.679 (April) 1927.

3 Chamberlain, W P, quoted by H Sewall. *Oxford Medicine*, vol 1, New York, 1927, p 491.

4 Balfour, Andrew. Effects of Tropical Climates, in Byam and Archibald's *The Practice of Medicine in the Tropics*, vol 1, London, Henry Frowde & Hodder and Stoughton, 1921, p 4.

5 Osgood, Edwin E. Hemoglobin, Color Index, Saturation Index and Volume Index Standards in Men, *Arch Int Med* **37** 685 (May) 1926.

by inaccurate and obsolete methods Bie and Moller<sup>6</sup> stated that the figures for normal red cell counts (5,000,000 in men and 4,500,000 in women) are based on the work of Vierorde (1852) and Welcher (1854), each of whom examined only two subjects Likewise, the variety of standards accepted as 100 per cent by the various hemoglobinometers reflects the inaccurate foundation on which they depend

#### SUBJECTS EXAMINED

The subjects of our examination were normal, healthy students between the ages of 20 and 30 years Each of these students has been the subject of a thorough laboratory examination during the course of the academic session, including urinalysis, renal function tests, gastric analysis, several examinations of the stools and even chemical examination of the blood The negative results of these examinations, along with a negative history, give us reason to believe that they were all free of organic disease A few of them were slightly "under par," judging by their height-weight ratio, and this was shown in their blood count They were, however, free of organic disease Eighty per cent were Americans born of American parents, the remainder were of French, Spanish, Italian or Russian descent All but 5 per cent were born in the United States The majority have resided in the South (Louisiana, Mississippi, Alabama, Texas, North Carolina, Florida, Oklahoma and Arkansas) most of their lives With the exception of a few who have been North during the summer vacation, all have resided continuously in this locality for the past three years The examinations were made during May and June (before, during and after college examinations) During the period of examination, the atmospheric temperature ranged approximately between 75 and 88 or 90 F

Many of the specimens of blood were drawn about noon, before and after lunch Others were drawn about 9 a m In this way, any possible effect of a diurnal variation of hemoglobin has been obviated

#### METHODS

Ten cubic centimeters of venous blood were drawn into a syringe containing 40 mg of finely powdered neutral potassium oxalate, and thoroughly mixed The blood so obtained was used for red cell counts, hemoglobin estimation and "blood volume" determinations The amount of oxalate used was found to have no effect on cell count or hemoglobin Its effect on blood volume is discussed under that heading

*Red Cell Counts*—Bass-Johns counting chambers and pipets (certified by the United States Bureau of Standards) were used Before using any sample of blood, care was taken to mix it thoroughly in order to avoid any error resulting from sedimentation Fresh Toison's solution was used for dilution and at least two dilutions of 1:200 were counted in each case Only results agreeing within

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<sup>6</sup> Bie, V., and Moller, P. Constitution du sang humain normal, Arch de mal du coeur, **15** 177 (April) 1922

100,000 cells were accepted, the average of two such closely agreeing figures being recorded. A number of red cell counts were made to determine any possible difference resulting from the use of venous blood as compared with blood obtained by finger puncture. Whenever care was taken to secure a free flow of blood from the finger (in order to prevent dilution resulting from the forcing out of serum in compressing the finger), counts made on blood obtained from the latter source were as high as those made on venous blood.

TABLE 1—*Hemoglobin Estimations by Newcomer and Van Slyke Methods*

Blood Number	Hemoglobin		
	Newcomer		Van Slyke Gm
	Per Cent	Gm	
1	100.3	16.97	18.16
2	95.3	16.12	17.46
3	92.0	15.57	16.99
4	78.0	13.20	15.08
5	70.9	12.00	14.19
6	69.3	11.73	13.82
7	63.8	10.89	13.53
8	61.8	10.46	12.40
9	53.7	9.09	10.53
10	53.0	8.97	10.48

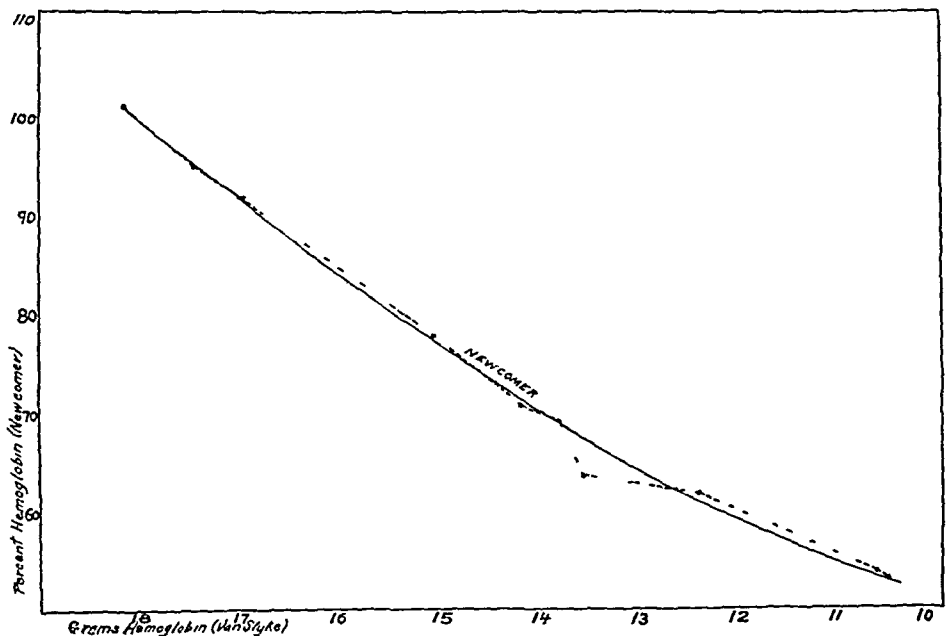


Fig 1—Correction curve for Newcomer hemoglobinometer. The straight line represents the correction curve and the dotted line represents the readings.

*Hemoglobin Estimation*—Prior to the commencement of our work on students, the accuracy of the generally used clinical methods of hemoglobin estimation (Sahli, Newcomer, Dare, Tallqvist) was tested, readings on the various instruments being compared with those obtained by van Slyke's method of determining the oxygen capacity of the blood.<sup>7</sup> All the instruments examined proved to be inaccurate. Readings on the Newcomer instrument, however, although lower than those obtained by the van Slyke method, proved to be consistently lower (table 1), so that it was found possible to plot a correction curve for our

<sup>7</sup> Van Slyke, D. D., and Stadie, W. C. The Determination of Gases of the Blood, *J. Biol. Chem.* 49:1 (Nov.) 1921.

Newcomer instrument (fig 1) As this instrument is readily available for clinical use and apparently accurate when corrected, it was chosen for our work Readings were not made until the acid hematin solution was allowed to stand for one-half hour A time correction according to the formula worked out by Newcomer<sup>8</sup> was made in each case

*Cell Volume*—Volume determinations were made by centrifugalization of 4 cc of blood at 3,500 revolutions per minute After an initial centrifugalization for from twenty to thirty minutes, readings were made at five minute intervals until the red cell volume did not show any change at two successive readings The centrifuge tube was made by sealing off the end of a 10 cc Mohr pipet and cutting it off a little above the 6 mark It was carefully recalibrated

#### RED CELL COUNTS IN NORMAL MALES

Red cell counts made with reasonably accurate care have been reported for 178 men between the ages of 19 and 30 years Biering<sup>9</sup> (Sweden) reported four men, averaging 5,050,000, Bie and Moller<sup>6</sup> (Denmark), ten men, averaging 5,530,000, Gram and Norgaard<sup>10</sup>

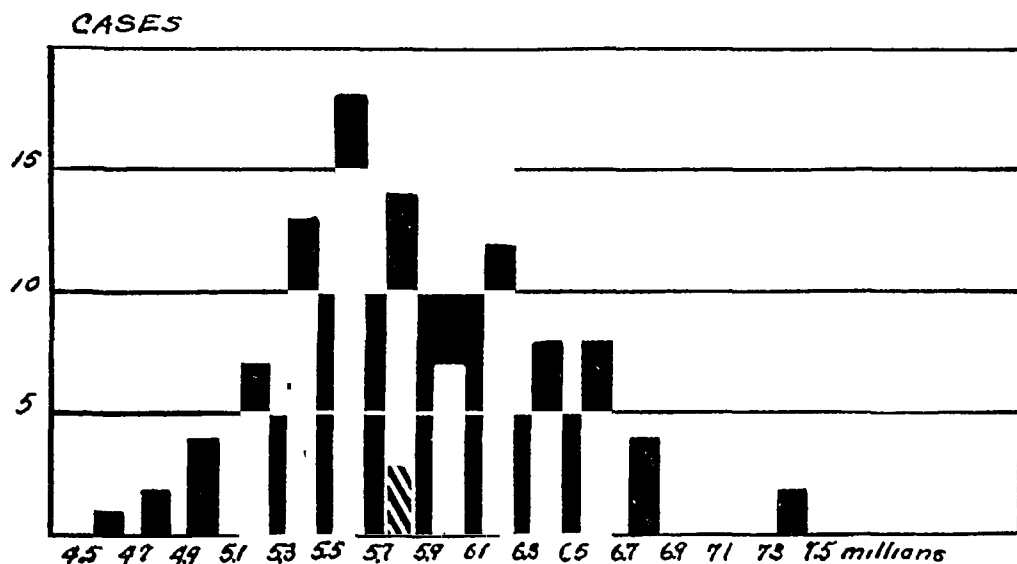


Fig 2—Red cell counts in 100 healthy young men The average occurs in columns with shaded lower portion

(Denmark), seven men, averaging 5,390,000, Haden<sup>11</sup> (Kansas City), twenty men, averaging 5,080,000, Osgood<sup>5</sup> (Oregon), 137 men, averaging 5,390,000, making a total of 178 men, averaging 5,410,000

8 Newcomer, H S A New Optical Instrument for the Determination of Hemoglobin, *J Biol Chem* **55** 569 (April) 1923

9 Biering, K Svingninger i erythrocyttallet hos normale mennesker, *Ugeskr f Laeger* **82** 1445 (Nov 18) 1920, quoted by Osgood

10 Gram, H C, and Norgaard, A Relation between Hemoglobin, Cell Count and Cell Volume in the Venous Blood of Normal Human Subjects, *Arch Int Med* **31** 164 (Feb) 1923

11 Haden, R L Accurate Criteria for Differentiating Anemias, *Arch Int Med* **31** 765 (May) 1927



A number of other counts which have been reported by other authors are tabulated by Bie and Moller<sup>6</sup> and by Osgood,<sup>3</sup> but none of these are sufficiently accurate to be included with the foregoing data

Our average in 100 men between the ages of 19 and 30 years was 5,850,000. Figure 2 shows that 95 per cent of our counts ranged between 5,000,000 and 6,900,000, while 64 per cent ranged between 5,300,000 and 6,300,000. Two students had counts above 7,000,000, while five had counts below 5,000,000. Neither of the former showed any clinical evidence of polycythemia, while all of the latter were slightly underweight although not suffering from any disease. All of these figures were included in computing our average.

Osgood, working in Oregon, found 90 per cent of the counts between 4,700,000 and 6,100,000. It is noteworthy that 36 per cent of our students had counts above 6,000,000, while only 7.3 per cent of Osgood's cases were above that figure.

When our figure of 5,850,000 is included with the 178 accurate counts already quoted, the average for the 278 persons is 5,570,000.

#### HEMOGLOBIN CONTENT OF THE BLOOD OF NORMAL MALES

A statement of the inaccurate foundation on which our methods of hemoglobin estimation (in themselves inexact) are based cannot be too often repeated. It is not generally known that the Sahli instrument accepts 17.2 Gm per hundred cubic centimeters of blood as 100 per cent, while the Dare is based on 13.8 Gm as the equivalent of 100 per cent, the Newcomer standard is 16.92 Gm, whereas the Tallqvist scale is set on a basis of 15.8 Gm. This wide range in the accepted standard is merely a reflection of the inaccurate basis on which these figures have been calculated. As a matter of fact, until Osgood<sup>12</sup> published his work, a sufficient number of accurate determinations on which to calculate a standard was not available. When one considers that hemoglobin varies not only with age, sex,<sup>13</sup> and time of day,<sup>14</sup> but also with altitude and perhaps climate and race, it is obvious that, for example, Haldane's<sup>15</sup>

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12 Osgood, Edwin E., and Haskins, Howard D. Relation between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women, *Arch Int Med* **39** 643 (May) 1927. Osgood (footnote 5).

13 Williamson, C. S. Influence of Age and Sex on Hemoglobin, *Arch Int Med* **18** 505 (Oct.) 1916.

14 Ward, H. C. The Hourly Variations in the Quantity of Hemoglobin and in the Number of Corpuscles in Human Blood, *Am J Physiol* **11** 394 (July) 1904. Dreyer, G., Bazett, H. C., and Pierce, H. F. Diurnal Variation in the Hemoglobin Content of the Blood, *Lancet* **199** 588 (Sept 18) 1920. Rabinowitch, I. M. Variation of Percentage of Hemoglobin in Man During Day, *J Lab & Clin Med* **9**:120 (Nov.) 1923.

15 Haldane, J. The Colorimetric Determination of Hemoglobin, *J Physiol* **26** 497 (June) 1901.

average of 13.8 Gm in twelve men in England (determined by a method that is now obsolete) cannot be taken as the basis for 100 per cent all over the world

Reliable hemoglobin estimations on healthy males between the ages of 19 and 30 years have been reported as follows: Williamson<sup>13</sup> (spectrophotometer), thirty-six men, averaging 16.8 Gm; Bie and Møller<sup>6</sup> (Meisling colorimeter, checked by oxygen apparatus of Peterson-Bohn), ten men, averaging 14.75 Gm; Giam and Nørgaard<sup>10</sup> (Autenreith-Königsberger colorimeter, corrected by oxygen method), seven men, averaging 14.89 Gm; Haden<sup>11</sup> (van Slyke's method), twenty men,

### CASES

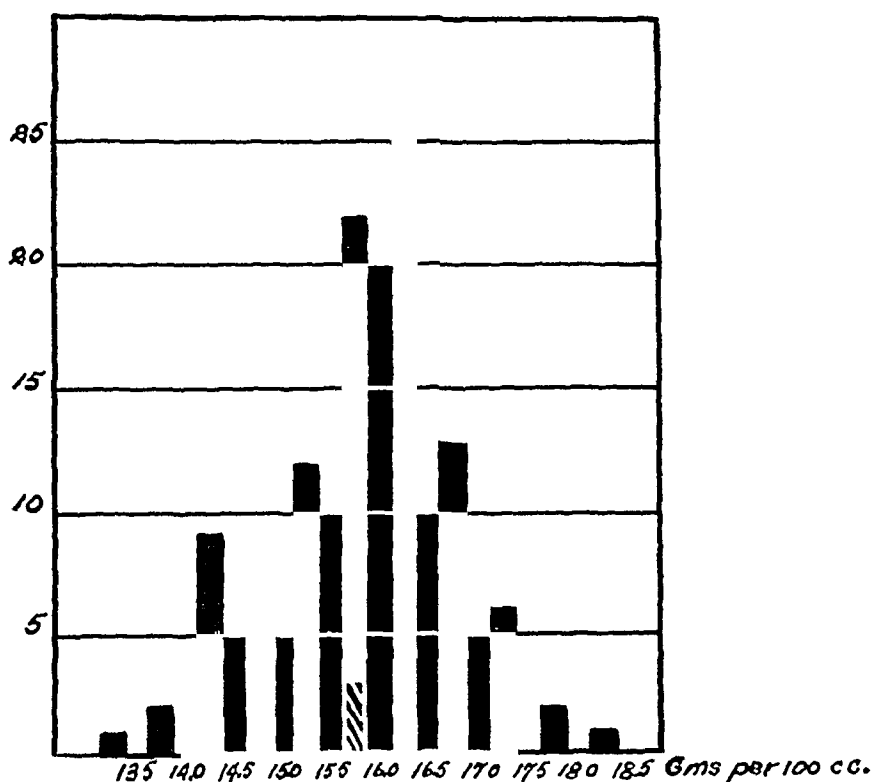


Fig. 3—Total hemoglobin in 100 healthy young men

averaging 15.83 Gm; Brown and Rowntree<sup>16</sup> (Palmer's method, checked by Osgood-Haskins' method<sup>17</sup>), seven men, averaging 16.27 Gm; Osgood<sup>5</sup> (Osgood-Haskins' method<sup>17</sup>), 137 men, averaging 15.76 Gm, making a total of 217 men, averaging 15.88 Gm.

This average agrees closely with our average of 15.87 Gm in 100 men. The average for the total of 317 estimations is 15.88 Gm. The

16 Brown, G. E., and Rowntree, L. G. The Volume and Composition of the Blood and the Changes Incident to Diuresis in Cases of Edema, *Arch Int Med* 35: 129 (Jan) 1925.

17 Estimations of hemoglobin by the Osgood-Haskins' method compare very closely to those obtained by the van Slyke method according to Osgood.

extremes in 171 of the foregoing 217 estimations were 13.3 and 19.46 Gm while our extremes were 13.4 and 18.3 Gm

Seventy-three per cent of our determinations ranged between 15 and 16.9 Gm (fig 3), while 87 per cent were between 14 and 16.9 Gm with only 10 per cent above that figure. It is interesting to note that 85 per cent of Osgood's <sup>5</sup> 137 estimations occurred between 14 and 16.9 Gm, with also 10 per cent above that figure

#### COLOR INDEX

As color index is an expression of the relation of hemoglobin to the number of erythrocytes—the percentage of hemoglobin in proportion to the percentage of cells—it is important that the hemoglobin figure taken as 100 per cent be calculated to a basis of 5,000,000 red cells, since that is the number of cells taken as 100 per cent in the calculation. Thus, if a study of normal figures should reveal that the average hemoglobin figure is 16.5 Gm in blood samples which on the average contain 5,500,000 red cells, then 15 Gm (16.5 calculated to a count of 5,000,000) should be taken as the 100 per cent on which percentage of hemoglobin used in the determination of color index is based. For the expression, "the number of grams of hemoglobin per 100 cc of blood calculated to a red cell count of 5 million per cu mm," Osgood <sup>5</sup> has suggested the term "hemoglobin coefficient." Before accurate color indexes can be calculated the normal average hemoglobin coefficient must be determined. It is this average hemoglobin coefficient, calculated on the basis of a large series of accurate determinations of hemoglobin and red cell counts, that should be used as 100 per cent by the various clinical hemoglobinometers.

We have been able to find only the following satisfactory data for the calculation of a standard hemoglobin coefficient for men between the ages of 19 and 30. Bie and Moller,<sup>6</sup> ten men, averaging 13.34 Gm, Gram and Norgaard,<sup>10</sup> seven men, averaging 13.82 Gm. Haden,<sup>11</sup> twenty men, averaging 15.57 Gm, Osgood,<sup>5</sup> 137 men averaging 14.66 Gm making a total of 174 men averaging 14.65 Gm.

Our average of 13.66 Gm in 100 men is considerably lower than that found by Haden or Osgood and corresponds to the observations of Gram and Norgaard and of Bie and Moller. Our low hemoglobin coefficient is the outcome of our higher average red cell count as our average hemoglobin figure is practically the same as that found by Haden and by Osgood.

The hemoglobin coefficient in 174 cases under our observations ranged between 12.32 and 18.63 Gm. Osgood found 90 per cent to occur between 13 and 16.5 Gm. Our coefficients ranged from 10.4 to 17.4

Gm, with 90 per cent between 12 and 16 Gm. Frequency figure 4 shows a definite peak in the region of the average.

The average of all these 274 determinations is 14.29 Gm. As this figure represents a wider range than that on which Osgood's hemoglobin coefficient (14.7) is based, we suggest that 14.3 Gm be accepted as the hemoglobin coefficient for normal men between the ages of 19 and 30 years. Recalculation of color indexes on this basis shows the average indexes to be as follows: Haden (Kansas City), twenty men, averaging 1.09, Osgood (Oregon), 137 men, averaging 1.02, Gram and Norgaard (Denmark), seven men averaging 0.97, Wintrobe and Miller (Louisiana), 100 men, averaging 0.95, Bie and Moller (Denmark), ten men, averaging 0.93, making a total of 274 men, averaging 1.

### CASES

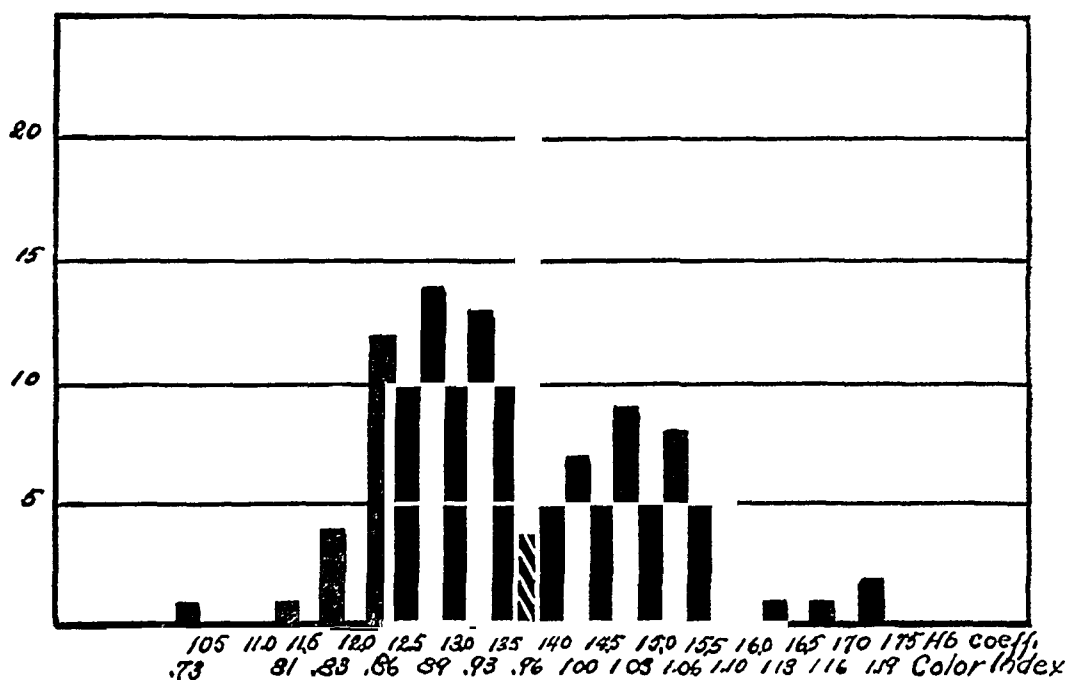


Fig. 4—Hemoglobin coefficients and color indexes in 100 healthy young men

Although the difference between these color indexes is relatively small, one is led to wonder whether or not the effect of climate is evidenced by this slight variation (fig. 5).

### TOTAL CELL VOLUME

In collecting venous blood for the determination of its red cell count, hemoglobin content and cell volume, it is important that a method be employed which leaves the blood undiluted and isotonic. The addition of heparin or hirudin fulfils these requirements, but has the disadvantage of being very expensive. When dry neutral potassium oxalate is used, the blood remains undiluted but a somewhat hypertonic solution is produced.

A number of experiments were carried out by the following method to determine the error resulting from the use of such a hypertonic solution. To 30 cc of blood, obtained by venous puncture, sufficient heparin was added to prevent clotting. Ten cubic centimeters of this

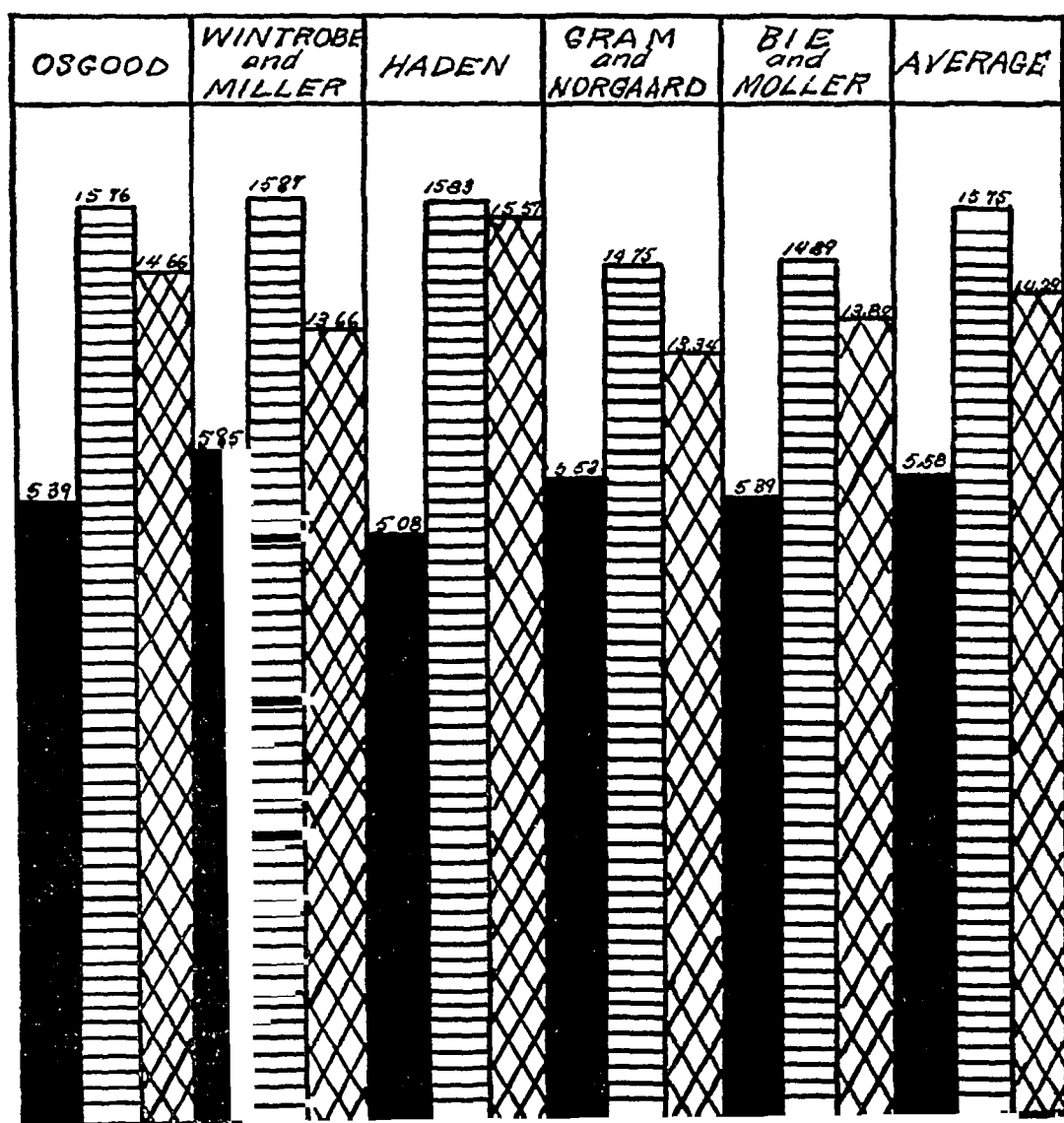


Fig 5—Cell counts and hemoglobin in different parts of the world on healthy young men. The black areas represent the red blood cells, the lined areas, the hemoglobin, and the cross-patched areas, the hemoglobin coefficient.

blood was set aside as a control. To another 10 cubic centimeters, 40 mg of neutral potassium oxalate was added and thoroughly mixed, while the remaining 10 cc was mixed with 20 mg of potassium oxalate. Red cell counts, hemoglobin and volume determinations were then carried out on each of these three samples by our usual methods.

Cell counts and hemoglobin values did not show an appreciable difference in any of the samples. A definite decrease of cell volume, however, was found to result from the production of a hypertonic solution.

Observations on the cell volume in two experiments are shown in table 2.

Our experiments showed that the addition of 20 mg. of neutral potassium oxalate to 10 cc. of blood (the proportion used by Osgood) caused an average shrinkage of cell volume of 3.68 per cent. This tallies closely with Osgood's figure of 3.5 per cent. The addition of 40 mg. of oxalate to 10 cc. of blood (the proportion employed in all our work) caused an average shrinkage of 6.7 per cent. As the heparin method is theoretically ideal, all of our volume figures have been corrected by adding 6.7 per cent.

Haden<sup>11</sup> reported volume determinations on twenty men between the ages of 19 and 30 years. He used 1.6 per cent sodium oxalate

TABLE 2—*Effect of Oxalate on Cell Volume*

	Experiment 1		Experiment 2	
	Per Cent of Cell Volume	Per Cent of Difference	Per Cent of Cell Volume	Per Cent of Difference
Heparinized blood without oxalate	49.7	0	49.2	0
Heparinized blood with 20 mg. oxalate added to 10 cc.	48.0	3.54	47.4	3.83
Heparinized blood with 40 mg. oxalate added to 10 cc.	46.7	6.42	46.0	6.98

solution and centrifugated at 2,500 revolutions per minute for one-half hour. As sometimes centrifugation to constant volume is not complete at the end of thirty minutes, some of his figures may be high. His average was 46.5 cc. of cells per hundred cubic centimeters of blood. Bie and Moller<sup>6</sup> used defibrinated blood and were careful to centrifugate to constant volume. Their average was 46.4 cc. Gram and Norgaard,<sup>10</sup> using the hirudin method, and centrifugating for one and a half hours at 3,000 revolutions per minute, found an average volume of 45.9 cc. in seven men. Osgood,<sup>5</sup> using the oxalate method, found an average of 44.84 cc. in ninety-four men. The addition of 3.5 per cent to this figure, to allow for shrinkage resulting from the use of 20 mg. oxalate with 10 cc. of blood, brings it to 46.4 cc. Whether, on account of their methods being a little questionable, the observations of Haden and of Bie and Moller be included, or not, the average cell volume, corrected to a basis of the figure obtained when the blood used is undiluted and isotonic, is 46.4 cc. With this figure our average of 46.5 cc., in 100 men, agrees closely. The average of the total of 231 determinations is 46.4 cc.

Frequency figure 6 shows that 85 per cent of our results ranged between 40 and 50 cc, with 54 per cent between 46 and 50 cc. This agrees closely with Osgood's figure of over 90 per cent between 40 and 50 cc and 56 per cent between 45 and 49 cc.

#### VOLUME INDEX

Capps<sup>18</sup> in 1903, introduced the term "volume index" to express the cell volume of a given sample of blood as compared with the normal. Its determination is similar to that of the color index with the difference that cell volume percentage is considered instead of hemoglobin percentage. A volume index of more than 1 is always present when the color index is greater than 1, and also in many instances in which the color index is less than 1. The volume index is not only of greater

#### CASES

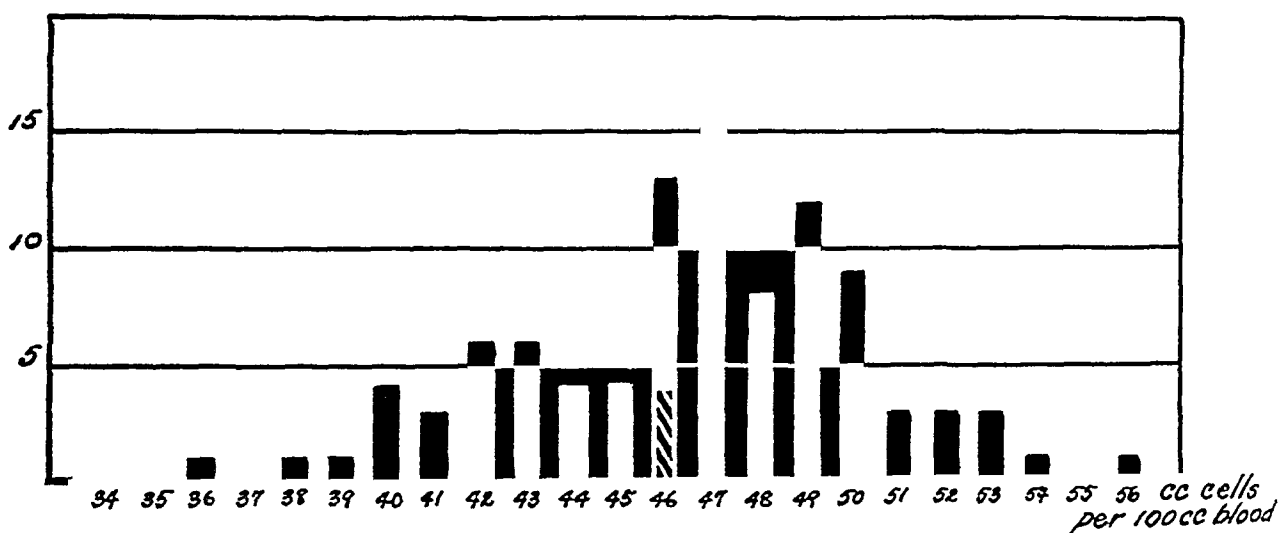


Fig 6—Total volume of cells in 100 healthy young men

value than the color index, but serves as an important check on it. As an accurate determination of cell volume is relatively easy to carry out, volume index determinations are of particular value as long as the generally used methods of hemoglobin determination remain as inaccurate as they now are.

The volume index is determined by dividing the percentage volume of cells (expressed as a percentage of the average normal volume for the given sex and age group and calculated to a count of 5,000,000 red cells) by the percentage of red cells (5,000,000 being 100 per cent). Osgood<sup>5</sup> has coined the term "volume coefficient" as a substitute for the expression, "volume of packed red cells per 100 cc of blood calculated to a red cell count of 5 million."

18 Capps, J. A. A Study of Volume Index, J. M. Research 5 367, 1903

Accurate data for the determination of volume coefficient are supplied by Gram and Norgaard,<sup>10</sup> whose average was 42.2 in seven men, and by Osgood,<sup>5</sup> whose average becomes 42.23 in ninety-four men, when a correction is made for the error resulting from the use of oxalate. The average of these 101 determinations is 42.23 cc. Our average (corrected for the use of oxalate) was 39.95 cc in 100 men. Our low volume coefficient is the result of our high average red cell count. The average for these 201 determinations is 41.09 cc. This agrees with the figure (41 cc.) originally suggested by Osgood as the normal volume coefficient for young men between the ages of 19 to 30 years.

Osgood does not consider the data given by Haden<sup>11</sup> (average volume coefficient of 45.8 in twenty men) or by Bie and Moller<sup>6</sup> (average of 42.0 in ten men) as being sufficiently accurate to be included. In any case, the addition of their observations does not greatly increase

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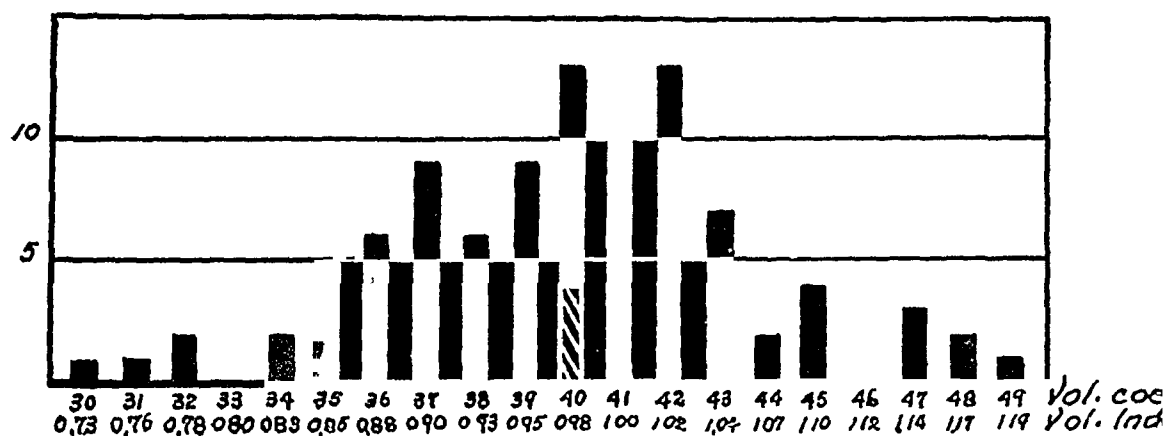


Fig. 7—Volume indexes and volume coefficients in 100 healthy young men

the average volume coefficient (the average for 231 men becomes 41.54 cc.)

Recalculation of average volume indexes from the data supplied by various authors, on the basis of a volume coefficient of 41 cc., reveals the following: Haden (Kansas City), twenty men, averaging 1.12; Osgood (Oregon), ninety-four men, averaging 1.05; Gram and Norgaard (Denmark), seven men, averaging 1.04; Bie and Moller (Denmark), ten men, averaging 1.02; Wintrobe and Miller (Louisiana), 100 men, averaging 0.97, making a total of 231 men, averaging 1.02.

Frequency figure 7 shows that our most frequently occurring volume coefficient was 41, corresponding to a volume index of 1. Our average was 39.7, corresponding to a volume index of 0.97. Seventy-seven per cent of our volume coefficients ranged between 37 and 45 cc., corresponding to volume indexes of 0.90 to 1.1, while 88 per cent fell between 35 and 45 cc., corresponding to volume indexes of 0.85 to 1.1. Osgood found 90 per cent between 37 and 45 cc., corresponding to volume



indexes of 0.9 to 1.1 and 98 per cent between 35 and 45 cc, corresponding to volume indexes of 0.85 to 1.1

#### SATURATION INDEX

It is a common impression that color index is an expression of the saturation of red cell with hemoglobin. This is of course not true, since color index is the expression of the relation of hemoglobin to the number of erythrocytes. To denote the relation of hemoglobin to volume of erythrocytes, Haden<sup>11</sup> has suggested a new index, the "saturation index," which expresses the ratio between the concentration of hemoglobin per unit volume of cells in a particular subject, and the average

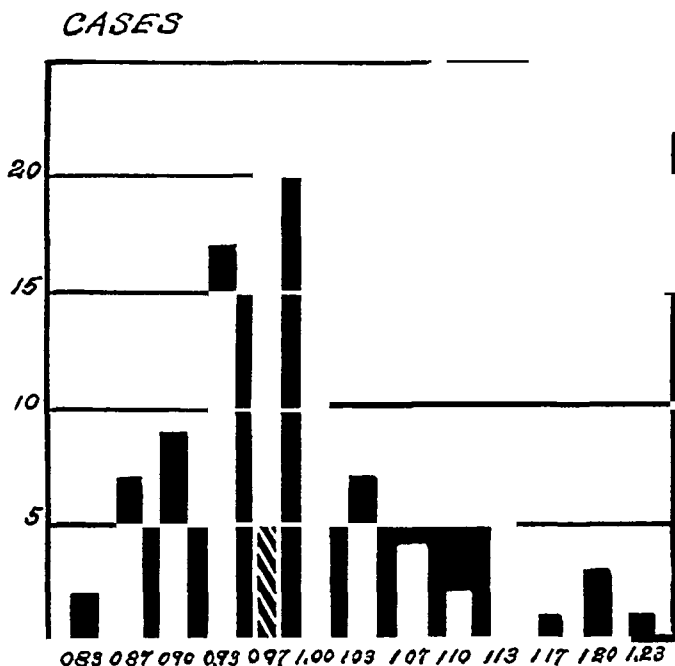


Fig. 8—Saturation indexes in 100 healthy young men

concentration of hemoglobin per unit volume of cells in normal subjects of the same sex and age group

Haden calculated the saturation index by dividing the color index by the volume index. Since this is the same as dividing the hemoglobin percentage by the volume percentage, and since in so doing one derives a clearer conception of the meaning of the saturation index, we suggest that the saturation index be defined as, "the proportion of hemoglobin per unit volume of cells, expressed in proportion to the normal," and be calculated by dividing hemoglobin per cent by volume per cent.

Only in normal blood, in which both the number and the volume of red cells are normal, are color index and saturation index synonymous. According to Haden, a supersaturation of red cells never occurs, and the saturation index never rises above 1.

The available data for normal men between the ages of 19 and 30 years, recalculated on the basis of a hemoglobin coefficient of 14.3 Gm and a volume coefficient of 41 cc, show the following average saturation indexes: Bie and Møller,<sup>6</sup> ten men, averaging 0.91; Gram and Norgaard,<sup>10</sup> seven men, averaging 0.93; Haden,<sup>11</sup> twenty men, averaging

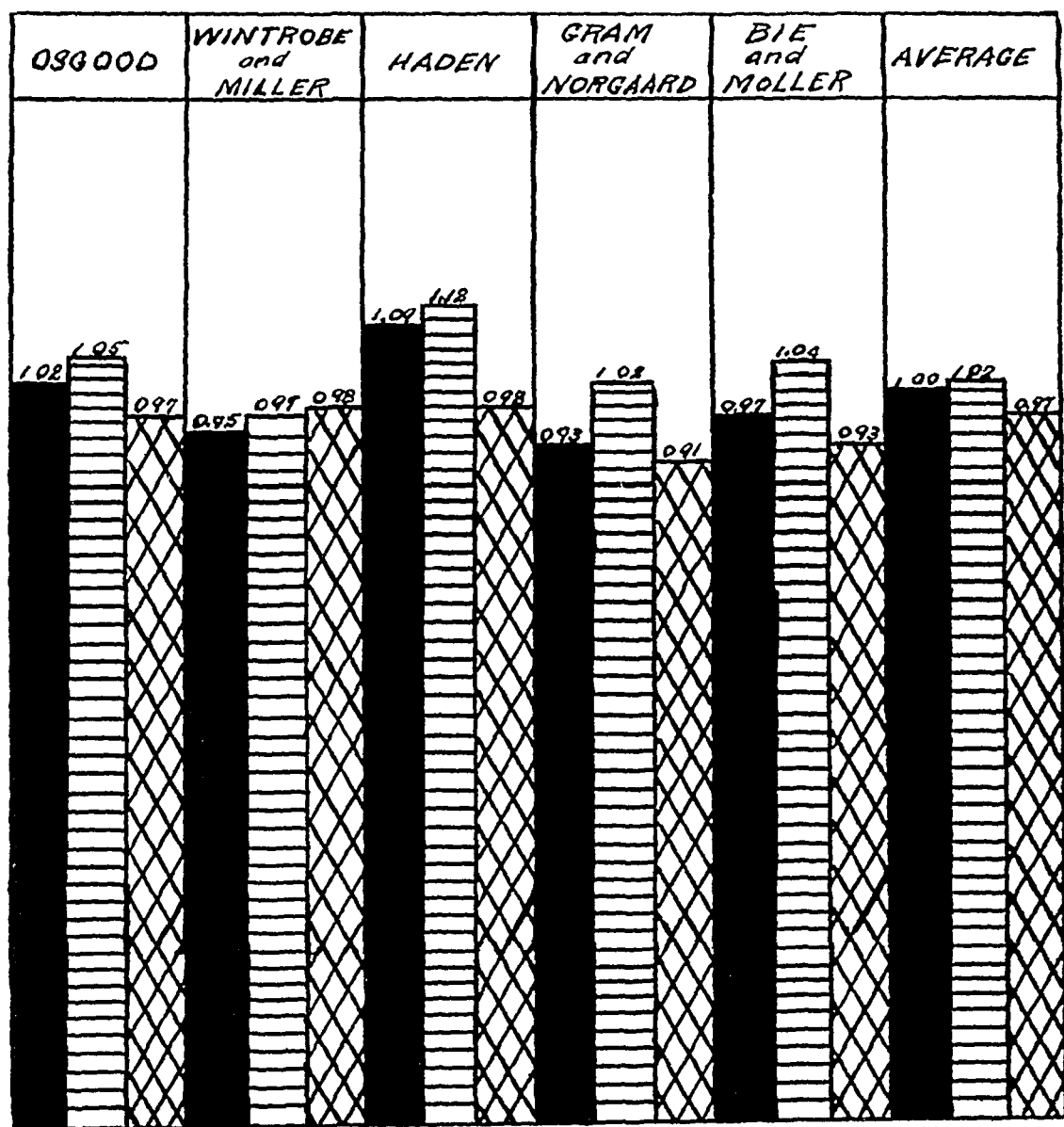


Fig. 9—Indexes in different parts of the world on healthy young men. The black areas represent the color index, the lined area represents the volume index, and the cross-patched area the saturation index.

0.98, Osgood,<sup>5</sup> ninety-four men, averaging 0.97, making a total of 131 men, averaging 0.97.

Our average for 100 men was 0.98. The average for the 231 men is 0.97.

Frequency figure 8 shows the frequency distribution of saturation indexes in our 100 men. It will be seen that the average and peak coincide. Eighty-one per cent of our saturation indexes occurred between 0.9 and 1.1, as compared with over 90 per cent of Osgood's saturation indexes falling within that range.

The method of determining the color, volume and saturation indexes is best illustrated by an example. A given sample of the blood of a man, aged 25, contains 5,850,000 red cells per cubic millimeter, 15.87 Gm of hemoglobin per hundred cubic centimeters, and 46.5 cc packed red cells per hundred cubic centimeters.

The percentage of hemoglobin is 15.87 divided by 14.3 (the hemoglobin coefficient for the given age group and sex) or  $\frac{15.87}{14.3} \times 100 = 111$  per cent.

The percentage of cells is  $\frac{5.85}{5.0} \times 100 = 117$  per cent.

Color index is  $\frac{\text{Hb \%}}{\text{RBC \%}}$ , or  $\frac{111}{117} = 0.95$ .

The cell volume percentage is 46.5 divided by 41 (volume coefficient for the given age and sex), or  $\frac{46.5}{41} \times 100 = 113.4$  per cent.

Volume index is  $\frac{\text{Vol \%}}{\text{RBC \%}}$ , or  $\frac{113.4}{117.0} = 0.97$ .

Saturation index is  $\frac{\text{Hb \%}}{\text{Vol \%}}$ , or  $\frac{111.0}{113.4} = 0.98$ .

TABLE 3—*Observations on the Blood in Healthy Young Men Between 19 and 30 Years of Age in Different Parts of the World.*

Author	Cases		Red Blood Cells in Mil lions	Hemoglobin		Blood Volume		Indexes		
				Gm	Coeffi- cient	Red Blood Cells per 100 Cc	Coeffi- cient	Color	Vol- ume	Satu- ration
	No	Location								
Osgood	137	Oregon	5.39	15.76	14.63	46.4	42.2	1.02	1.05	0.97
Wintrobe and Miller	100	Louisiana	5.85	15.87	13.66	46.5	39.7	0.95	0.97	0.93
Haden	20	Kansas City	5.08	15.83	15.57	46.5	45.8	1.09	1.12	0.98
Bie and Moller	10	Denmark	5.53	14.75	13.34	46.4	42.0	0.93	1.02	0.91
Gram and Norgaard	7	Denmark	5.39	14.89	13.82	45.9	42.2	0.97	1.04	0.93
Average			5.58	15.75	14.29	46.4	41.5	1.00	1.02	0.97

\* Calculations are based on a hemoglobin coefficient of 14.3 Gm and a volume coefficient of 41 cc.

TABLE 4—*Observations on the Blood in One Hundred Normal Young Men*

Sub- ject	Age	Red Cell Count, Millions per C Mm	Hemo- globin, Gm per 100 Cc	Hemoglo- bin per 100 Cc per 5 Million Cells	Color Index	Volume of Cells per 100 Cc	Volume of Cells per 100 Cc per 5 Million	Volume Index	Situ- ration Index
1	19	5.48	13.40	12.30	0.86	45.9	41.9	1.02	0.84
2	24	5.69	14.50	12.70	0.89	34.1	30.0	0.73	1.22
3	22	5.59	15.25	13.64	0.95	41.5	37.1	0.91	1.01
4	24	6.61	16.20	12.30	0.86	49.7	37.6	0.92	0.91
5	21	6.09	16.05	13.50	0.93	50.1	41.2	1.00	0.93
6	22	5.54	16.60	15.00	1.05	47.9	43.2	1.05	1.00
7	23	6.03	16.20	13.40	0.94	47.6	39.5	0.97	0.97
8	27	5.20	16.20	15.60	1.09	46.9	45.1	1.10	0.99
9	27	4.68	15.93	17.06	1.18	40.2	42.9	1.05	1.12
10	28	5.88	16.05	13.65	0.95	45.8	39.0	0.95	1.00
11	23	5.40	16.75	15.50	1.09	48.4	44.8	1.08	1.01
12	22	5.53	18.30	16.50	1.16	46.6	42.2	1.02	1.12
13	22	5.32	16.75	15.70	1.10	51.5	48.4	1.18	0.93
14	21	4.70	16.33	17.40	1.21	36.4	38.7	0.95	1.26
15	22	5.84	17.02	14.50	1.02	40.2	34.5	0.84	1.20
16	24	5.32	16.90	15.90	1.11	45.3	42.7	1.03	1.06
17	21	5.37	16.05	15.00	1.04	38.9	36.2	0.89	1.16
18	20	5.58	17.25	15.40	1.08	43.5	39.0	0.95	1.13
19	25	6.53	17.25	13.20	0.92	48.1	36.8	0.90	1.02
20	25	5.14	15.65	15.20	1.06	43.3	42.1	1.03	1.02
21	23	5.64	14.80	13.10	0.92	47.9	42.5	1.03	0.88
22	21	5.62	16.00	14.20	1.00	45.9	40.8	1.00	1.00
23	22	5.99	15.95	13.30	0.93	37.9	31.7	0.77	1.20
24	25	6.15	16.60	13.50	0.94	47.2	38.4	0.94	1.00
25	21	6.67	16.35	12.30	0.86	43.2	31.9	0.79	1.09
26	21	5.46	16.25	14.90	1.04	49.1	44.9	1.09	0.95
27	23	5.27	15.80	15.00	1.05	49.0	46.6	1.13	0.92
28	23	4.98	16.05	16.30	1.13	47.1	47.3	1.15	0.98
29	23	5.18	15.24	14.70	1.03	50.5	48.8	1.19	0.87
30	21	6.69	16.20	12.10	0.85	46.8	35.0	0.85	1.00
31	21	5.58	16.05	14.56	1.00	46.3	41.6	1.00	1.00
32	24	6.71	17.50	13.00	0.91	56.6	42.2	1.03	0.88
33	26	5.80	15.23	13.10	0.92	45.5	39.3	0.96	0.96
34	24	5.71	15.38	13.50	0.94	45.5	39.9	0.98	0.96
35	25	5.24	15.77	15.00	1.05	41.0	39.2	0.96	1.09
36	28	5.45	16.65	15.30	1.07	48.9	44.9	1.09	0.98
37	24	5.57	16.95	15.20	1.06	46.2	41.5	1.01	0.99
38	24	5.75	16.27	14.10	0.99	43.0	37.5	0.92	1.08
39	24	5.52	15.25	13.80	0.97	47.4	43.0	1.04	0.92
40	25	6.12	16.48	13.50	0.94	47.3	38.7	0.95	0.99
41	22	5.86	16.25	13.90	0.97	47.4	40.4	0.99	0.98
42	24	6.21	15.93	12.80	0.90	43.6	35.2	0.85	1.06
43	21	5.30	15.45	14.60	1.02	46.7	44.0	1.06	0.95
44	22	5.97	15.48	13.00	0.91	48.7	40.8	1.00	0.91
45	23	5.55	16.00	14.40	1.00	45.0	40.6	0.99	1.01
46	22	6.33	15.93	12.60	0.88	52.6	41.5	1.01	0.86
47	23	6.23	16.75	13.40	0.94	48.8	39.2	0.96	0.98
48	25	6.41	16.00	12.50	0.87	50.1	39.2	0.96	0.91
49	23	5.94	16.40	13.80	0.97	47.5	40.0	0.98	0.99
50	23	5.74	15.94	13.90	0.97	39.5	34.4	0.84	1.15
51	23	7.35	17.85	12.10	0.85	54.4	37.0	0.91	0.94
52	23	6.57	16.70	12.70	0.89	48.4	36.9	0.90	1.00
53	21	6.19	16.55	13.40	0.94	52.2	42.2	1.02	0.91
54	23	7.53	15.70	10.40	0.73	47.2	31.3	0.76	0.96
55	25	6.64	16.00	12.00	0.84	48.7	36.7	0.90	0.94
56	25	6.88	17.35	12.60	0.88	49.4	35.9	0.88	1.00
57	25	6.61	16.10	12.20	0.85	52.9	40.0	0.95	0.86
58	24	6.35	16.10	12.70	0.89	50.5	39.8	0.97	0.92
59	23	6.36	15.80	12.40	0.87	45.4	35.8	0.88	1.00
60	24	6.46	17.60	13.60	0.95	51.9	40.2	0.98	0.97
61	25	5.09	14.50	14.20	1.00	41.5	40.8	1.00	1.00
62	27	6.29	17.50	13.90	0.97	44.3	35.3	0.87	1.12
63	26	6.24	14.80	11.90	0.83	45.5	36.5	0.90	0.93
64	23	4.82	14.30	14.80	1.04	40.3	41.8	1.01	1.02
65	22	5.35	15.60	14.60	1.02	44.8	41.9	1.02	1.00
66	23	5.87	15.22	13.00	0.91	42.1	35.9	0.89	1.03
67	30	6.24	16.00	13.30	0.93	51.6	41.4	1.01	0.92
68	25	5.68	15.50	13.90	0.97	48.3	43.3	1.04	0.92
69	21	4.94	15.40	15.60	1.09	47.0	47.6	1.16	0.93
70	22	6.18	16.05	13.00	0.91	50.5	40.9	1.00	0.91
71	22	6.34	16.05	12.60	0.89	52.7	41.6	1.00	0.89
72	22	6.13	15.50	12.70	0.89	42.0	34.3	0.84	1.06
73	21	5.55	15.65	14.10	0.99	47.9	43.2	1.04	0.94
74	21	5.44	15.85	14.60	1.02	46.0	42.3	1.03	0.99
75	21	5.86	16.20	13.80	0.97	48.9	41.7	1.01	0.96
76	28	5.65	14.30	12.70	0.89	41.9	37.1	0.91	0.98
77	27	5.86	13.70	11.70	0.82	47.3	40.4	0.99	0.83
78	24	5.88	13.75	12.80	0.90	45.8	42.6	1.03	0.96

TABLE 4—*Observations on the Blood in One Hundred Normal Young Men—Continued*

Sub ject	Age	Red Cell Count, Millions per C Mm	Hemo- globin, Gm per 100 Cc	Hemoglo- bin per 100 Cc per 5 Million Cells	Color Index	Volume of Cells per 100 Cc	Volume of Cells per 100 Cc per 5 Million	Volume Index	Satu- ration Index
79	24	6 21	14 30	11 20	0 81	46 0	37 0	0 91	0 90
80	21	5 78	14 35	12 40	0 87	47 3	40 9	1 00	0 87
81	21	6 31	15 65	12 40	0 87	51 0	40 5	0 99	0 88
82	25	5 89	16 20	13 80	0 96	47 4	40 3	0 98	0 96
83	24	6 11	16 20	13 20	0 93	49 4	40 4	0 99	0 94
84	23	6 89	16 42	11 90	0 83	49 2	35 7	0 88	0 96
85	30	5 96	16 23	13 70	0 96	48 7	40 8	1 00	0 97
86	24	6 00	16 33	13 70	0 96	50 3	42 0	1 02	0 94
87	22	6 79	16 75	12 30	0 86	50 2	37 0	0 91	0 96
88	28	5 17	14 20	13 70	0 96	41 5	40 2	0 98	0 98
89	25	5 57	15 85	14 20	0 99	45 8	41 2	1 00	0 99
90	30	5 39	16 42	15 20	1 06	50 3	46 7	1 13	0 94
91	21	5 90	15 18	12 90	0 90	41 1	34 8	0 86	1 05
92	23	6 60	17 00	12 90	0 90	51 0	38 7	0 95	0 95
93	27	5 78	15 80	13 70	0 96	48 7	42 2	1 02	0 93
94	24	5 13	14 30	13 90	0 98	42 6	41 5	1 00	0 98
95	25	5 61	15 30	13 60	0 95	42 9	38 3	0 94	1 01
96	29	6 44	15 24	11 80	0 83	46 2	35 9	0 88	0 96
97	26	5 38	14 65	13 70	0 96	40 9	38 3	0 94	1 02
98	29	5 68	14 45	12 70	0 89	42 9	37 8	0 93	0 96
99	21	5 61	14 36	12 80	0 89	46 9	41 8	1 01	0 88
100	28	5 01	14 30	14 30	1 00	44 3	44 2	1 07	0 91
Average		5 85	15 87	13 65	0 96	46 5	39 9	0 97	0 98

## SUMMARY

1 The average red cell count in 100 healthy young men between 19 and 30 years of age was 5,850,000, with 95 per cent between 5,000,000 and 6,900,000. In contrast to this, Osgood, in Oregon, found an average of 5,390,000 with 90 per cent between 4,700,000 and 6,100,000.

2 The average total hemoglobin per hundred cubic centimeters of blood in 100 young men was 15 87 Gm, with 87 per cent between 14 and 16 9 Gm. Osgood found an average of 15 76 Gm with 90 per cent between 14 and 18 Gm.

3 Our average hemoglobin coefficient was 13 66 Gm per hundred cubic centimeters of blood. Osgood found an average coefficient of 14 66 Gm.

4 Our average color index was 0 95, while the average volume index was 0 97. A slight difference between the color and volume indexes, calculated from data obtained in different parts of the world, is noted.

5 The average total volume of packed red cells in 100 young men was 46 5 cc per hundred cubic centimeters of blood. Osgood found an average of 46 4 cc in ninety-four young men.

6 Our average volume coefficient was 39 95 cc per hundred cubic centimeters of blood. Osgood found an average coefficient of 42 23 cc.

7 It is suggested that the saturation index be defined as "the proportion of hemoglobin per unit volume of cells, expressed in proportion to the normal" and be calculated by dividing per cent of hemoglobin by per cent of volume.

## CONCLUSIONS

Accurate blood determinations in the South as compared with similar determinations made in other parts of the world showed a somewhat higher red cell count, with hemoglobin content and volume of packed red cells practically the same as elsewhere. The hemoglobin and volume coefficients were somewhat lower, as were also the color and volume indexes.

The normal blood figures for healthy young men between 19 and 30 years of age, calculated from several hundred accurate determinations made in different parts of the world, are 5,570,000 red cells, 15.88 Gm of hemoglobin per hundred cubic centimeters of blood and 46.4 cc of packed red cells per hundred cubic centimeters of blood. The average hemoglobin coefficient of 14.3 Gm per hundred cubic centimeters of blood should be used as 100 per cent by the various clinical hemoglobinometers, while the average volume coefficient of 41 cc per hundred cubic centimeters of blood may be taken as 100 per cent in the calculation of volume index.

# EXPERIMENTAL BILE PERITONITIS AND ITS TREATMENT IN THE DOG\*

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Bile peritonitis has been the subject of much discussion. Some writers have denied that bile plays any rôle in the production of the symptoms that accompany rupture of the gallbladder or bile ducts and have attributed the serious effects to bacterial action.

## CLINICAL LITERATURE

Buchanan summarized the literature on bile peritonitis without evident perforation of the biliary tract and came to the conclusion that there were no typical symptoms or signs and that there was insufficient evidence to make such a diagnosis even after operation or post mortem.

Many theories have been advanced as to the cause of this condition. Clairmont and von Hoberer's filtration theory, Newaverch and Luebke's microscopic perforation, Lich and Fraenkel's small almost invisible perforation, a rupture subsequently healed, rupture of the interhepatic bile canal of Newaverch, and postperitoneal perforation of the common duct.

Keene, Da Costa, Judd and Burden, Le Jars, Cumston and Pincoffs and Boggs concluded that bile will do little damage to the peritoneum unless infection is present. Nevertheless, Keene stated that death usually follows within twenty-four hours when there is a traumatic rupture of the gallbladder. Ochsner thought that the serious symptoms are due to fibroplastic peritonitis.

Gosset, Desplas and Bonnet reviewed 111 cases, mostly spontaneous perforation of the gallbladder into the peritoneal cavity, in which operation was performed. The mortality was 52.2 per cent. They stated that perforation of the gallbladder is much more serious than perforation of gastric or duodenal ulcer. The diagnosis is more difficult to make because the clinical symptoms are more rarely met. Meissner reported twelve cases of rupture of the common duct with eight deaths and seven cases of rupture of the hepatic ducts, with five deaths.

## EXPERIMENTAL LITERATURE

Clairmont and von Hoberer occluded the common duct experimentally in dogs and reported that four had died with intraperitoneal bile effusion without perforation of the bile tract. Bacteriologic reports were not

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\* From the Hull Physiological Laboratories of the University of Chicago.

given Fraenkel and Kiaus used aseptic technic. They did not find any ill effects from opening the gallbladder by laparotomy in guinea-pigs and rabbits, but added that the unsutured wound of the gallbladder cicatrized, and that there were quite a few adhesions about it, they attribute the chief rôle to bacteria.

Whole bile was injected intraperitoneally into rabbits by Bunting and Brown, they found that from 0.25 to 0.5 cc per kilogram killed the animals in twenty-four hours. Sellards injected autobile and heterobile intraperitoneally into rabbits weighing 1,000 Gm and found that 15 cc caused death in a few hours. He also had the same results with guinea-pigs.

Sellards injected beef bile and a bile salt, sodium glycocholate, which had been sterilized in an autoclave, intraperitoneally into rabbits and guinea-pigs, and found that death occurred in from eight to fifteen hours. The bile salt solution used was from 5 to 13 per cent. This strength is excessive, for these salts do not occur in that strength in hepatic bile. Also, the whole bile used was from a different type of animal.

#### ANALYSIS OF PROBLEM

The questions that naturally arise are in regard to the effect of autogenous bile free in the peritoneal cavity, whether bacteria are the sole harmful agents or whether they do not have any relation to the symptoms and the condition found at autopsy in bile peritonitis, what will be the effect of bile continuously pouring out into the peritoneal cavity, what difference in symptoms will be produced by varying the quantity of bile and what effect will bile from other dogs injected into the peritoneal cavity produce.

#### METHODS

1 All experiments were performed on dogs anesthetized with ether and operated on aseptically. The abdomen was opened along the edge of the right rectus muscle, the tip of the gallbladder caught up with forceps, a purse-string suture placed about the tip, and then the gallbladder was opened, letting the bile spill out into the peritoneal cavity, the opening was then closed with the purse-string suture, the edges of the bladder being inverted. The intestines were moved about to insure thorough distribution of the bile over the peritoneum, and the abdomen was closed. General symptoms were noted, and various tests applied as indicated.

2 An intraperitoneal fistula of the gallbladder was made aseptically under ether anesthesia. The bile was spilled into the peritoneal cavity and stirred about so that it would come into contact with much of the peritoneum. The edges of the opening in the gallbladder were stitched back, to prevent spontaneous closure, and the abdomen closed.



3 Bile was removed aseptically from the gallbladders of living dogs under anesthesia with a syringe and needle. Bile was collected from eight to twelve dogs, mixed, culture taken, and immediately injected by paracentesis into the peritoneal cavity of dogs, the quantity for single dosage being varied and repeated small doses also being given to other dogs. Part of the bile was sterilized in an autoclave at 15 pounds pressure for thirty minutes before injection.

#### 1 THE EFFECT OF BILE FROM THE GALLBLADDER SPILLED INTO THE PERITONEAL CAVITY

The animal was operated on, February 17. There was slight postoperative vomiting, the animal was fed the second day. Food and water were both retained, the animal was rather thirsty, it was up and walking about and ill effects were not apparent, the urine showed a slight trace of bile, and no albumin or sugar, the actions were entirely normal. On May 5, the dog was killed so the pathologic effects of the bile could be noted. At autopsy, the dog was well nourished and in excellent condition. An entirely normal condition was found, except that there were a few adhesions about the tip of the gallbladder where the incision had been made. Cultures were made from the bile at the time of operation and from the peritoneal cavity at autopsy. At operation, staphylococci were found in one case and a bacillus in another. Bacteria were not found at autopsy in any case.

#### 2 THE EFFECT OF BILE CONTINUOUSLY POURING OUT INTO THE PERITONEAL CAVITY

Dog 6—The animal weighed 10 Kg, a fistula of the gallbladder was made. The animal vomitted frequently, severe retching occurred, thirty minutes later there was a bowel movement. Later, frequent watery stools were passed, seven hours later, the animal staggered and was much weaker and rather listless, fifteen hours later, the heart was irregular and slow and the respirations slow and sluggish. The dog was hardly able to stand, and gradually became weaker and passed into coma, it did not have convulsions, was difficult to arouse and passed frequent bloody stools, twenty-two hours later, it died in coma, no urine was passed. At autopsy, the lungs were slightly congested in spots, the heart was soft and flabby, the peritoneal cavity contained 275 cc of slightly bloody fluid deeply stained with bile and a few gelatinous masses. The peritoneum was stained yellow, but this was most marked in the diaphragmatic portion, the peritoneum of the lesser omental cavity was also stained, the liver was markedly congested, bile was not found in the ducts or bladder, the lumen of the gallbladder was open. The intestines were covered with many small petechiae, which were most plentiful over the ileum, the intestines did not contain bile, the mucosa of the colon and small intestines was markedly congested, and the contents of the colon watery and bloody, the greater omentum was stained deep yellow and contained numerous petechiae. The kidneys were congested and bluish-red, the urinary bladder contained 2 cc of heavy bile colored urine, the chemical tests showed much bile and 5 per cent of albumin. Microscopic examination showed many red blood cells, few white blood cells, also renal cells and debris, cultures were negative.

Dog 4—A fistula of the gallbladder was made. The animal continued to vomit intermittently for four days, especially soon after eating or drinking. On the fifth day vomiting ceased and recovery was rapid. The urine for the first twenty-four hours contained much albumin and bile pigment which continued heavy for six

days and then gradually diminished, the bile disappearing first. The dog was killed sixty-eight days following operation. At autopsy, the greater omentum was adherent over the liver and the small and large intestines, when it was dissected away, the lobes of the liver were found firmly bound together, when these lobes were separated a sac was opened which contained 10 cc of bile, this communicated directly through the patent lumen into the gallbladder and ducts, all cultures were negative, the urine obtained at autopsy was normal.

Dog 8—A fistula of the gallbladder was made. The animal vomited some and had diarrhea for forty-eight hours. On the third day marked edema of the eyelids and lips occurred, as well as anasarca of the subcutaneous tissues of the body, on the third day the edema had diminished somewhat, the urine showed albumin, 5 per cent, many red blood cells, a few white blood cells, much debris and some bile. On the seventh day, the animal was sluggish and moved only when poked. The urine showed albumin and bile, the stool contained bile. The animal died eleven days after operation. At autopsy, the dog was markedly emaciated. There was 50 cc of bile colored fluid in the peritoneal cavity, partial closure of the lumen in the gallbladder was caused by adhesions of the edges of the liver, leaving only a needle-like opening through which bile passed into the peritoneal cavity, the bile ducts were patent, bile was present in the intestinal contents, the intestinal serosa was congested, the kidneys were congested, the greater omentum was much atrophied, but was adherent to the edge of the liver, cultures were negative.

#### SUPPLEMENTARY OPERATION

In addition to the operation used in method 2, a supplementary operation was made in which the common duct was doubly ligated and sectioned. This, of course, would cause all the bile to flow from the liver to the gallbladder and out into the peritoneal cavity. The symptoms were similar to those reported for dog 6. Two dogs were used, 14 and 15, each of about the same weight. Both died twenty-three hours after the operation. The conditions found at autopsy were similar. In dog 14, the bacteriologic culture of the peritoneal fluid was negative. In dog 15, *Bacillus coli* was obtained on culture.

Double ligation and section of the common duct only was used in dog 11. The animal progressed favorably as if nothing had been done, on the sixteenth day, it jumped off a table 32 inches high and within a few minutes appeared to be in distress and the abdominal muscles became tense. This was soon followed by vomiting and the other symptoms of bile peritonitis. Death occurred twenty-four hours later. The condition found at autopsy was typical of bile peritonitis, a small perforation of the common duct 1 inch (2.5 cm) above the ligature permitted bile to flow freely into the peritoneal cavity when the gallbladder or hepatic ducts were compressed. Diagnosis in this case was indirect traumatic rupture of the distended common duct followed by bile peritonitis, which is a condition similar to obstruction of the common duct by stone or tumor, with distention of the gallbladder and ducts in man, with rupture from slight trauma followed by peritonitis.

A few days later Dr. Ivy observed a similar acute onset of symptoms in a dog with which he was working. The dog died within twenty-four hours, and at autopsy showed a ruptured bile duct.

In section 2 it has been shown that bile is toxic and will produce death. The following technic was devised to determine the quantity of bile necessary to kill when free in the peritoneal cavity. As the dogs varied so much in weight, all injections were made on the basis of weight, so many cubic centimeters per kilogram of body weight.

## 3 THE EFFECT OF INTRAPERITONEAL INJECTION OF BILE

DOG 13—Into an animal weighing 4.2 Kg, 25.2 cc of bile from the gallbladder was injected intraperitoneally, 6 cc per kilogram of body weight. The symptoms were similar to those in the foregoing cases, but progressed more rapidly, death occurred in fifteen hours. The conditions found at autopsy were similar except that there was more clotted blood in the peritoneal cavity. Cultures were negative.

DOG 17—An animal weighing 4 Kg was given 20 cc of bile from the gallbladder intraperitoneally, 5 cc per kilogram of body weight. The symptoms were similar to those in the foregoing cases, death occurred ten hours after the injection. The condition found at autopsy also was similar to that found in the foregoing cases. Culture showed *B. coli* contamination.

DOG 33—Into an animal weighing 18 Kg, 90 cc of bile from the gallbladder was injected intraperitoneally, 5 cc per kilogram of body weight. The usual symptoms and condition were found at autopsy. The animal died after eleven and a half hours. Cultures were negative.

DOG 34—Into an animal weighing 12 Kg, 60 cc of bile was injected intraperitoneally, 5 cc per kilogram of body weight. The usual symptoms and condition were found at autopsy. The dog died after eleven and a half hours. Cultures were negative.

## EFFECT OF SUBLETHAL DOSE GIVEN INTRAPERITONEALLY

DOG 23—Into an animal weighing 4.2 Kg, 16.8 cc of bile from gallbladder was injected intraperitoneally, 4 cc per kilogram of body weight. There was immediate spasticity of the abdominal muscles, and the dog appeared to be in distress. (Intraperitoneal injections of physiologic sodium chloride solutions did not cause rigidity and only slight pain when paracentesis was performed.) Five minutes later, defecation and retching occurred. Ten minutes later vomiting and staggering were noticed, the retching and vomiting were repeated every few minutes—this was accompanied by thirst and lapping of water and frequent stools which became watery and then bloody. Nine hours later, there was marked edema of the eyelids and lips, a small amount of urine was passed, which contained bile and a trace of albumin, the heart was slow and irregular, respirations were slow. Eighteen hours later, the condition had returned practically to normal except for anuria. Thirty hours later, the urine showed bile and much albumin, some edema of the eyelids occurred. On the seventh day, the condition was good except for slight fluctuating edema of the eyelids, the urine showed bile and albumin. On the twenty-eighth day, edema of the eyelids persisted, the urine showed albumin in varying amounts. On the thirty-first day, the animal died. Autopsy showed many patches of bronchopneumonia in the lungs, the heart was flabby, 50 cc of bile colored peritoneal fluid was obtained, the liver showed a nutmeg appearance, the kidneys were congested, the suprarenals were diminished, especially the medulla.

DOG 42—Into an animal weighing 3 Kg, 6 cc of bile from the gallbladder was injected intraperitoneally, 2 cc per kilogram of body weight. The symptoms were the same as in the foregoing cases, but were less severe. Twenty-four hours later, the condition was normal, except the urine contained bile and albumin, the albumin gradually diminished, none was found on the seventh day. The dog was normal two months after injection.

## INFLUENCE OF BACTERIA

In a few instances, bacterial growths were obtained from the bile of other dogs used for these injections. Bacteria were also obtained from the peritoneal fluid following death of the dog into which bile had been injected, the cultures contained staphylococci or colon bacilli. The bacteria in most instances certainly could not cause the symptoms and death as the same reactions were obtained in dogs in which bacteria were not found in the bile used or in the peritoneal fluid at postmortem. Nevertheless, for evidence on this point, the following experiment was done.

Dog 30—Into an animal weighing 16 Kg. 8 cc of sterilized bile was injected intraperitoneally, 5 cc per kilogram of body weight. Death occurred in twenty-two hours. The symptoms and the condition found at autopsy were the ones usually seen. Cultures were negative.

## SUMMARY

Bile from the gallbladder was spilled into the peritoneal cavity in twenty-five dogs. There were no deaths, and the effects were slight and transitory. Some of the dogs vomited, a few had diarrhea, and the urine contained varying amounts of bile pigment. The amount of jaundice present was just perceptible. Bacteria were not the cause of these symptoms, as sterile or infected bile gave the same results.

Intraperitoneal fistula of the gallbladder in seven dogs permitted sufficient bile to pass into the peritoneal cavity to cause death within twenty-four hours. If the fistula was partly closed, the dog lived longer, and if it was completely closed early, the effects were transitory. The symptoms preceding death were bradycardia, low blood pressure, slow respiration, anuria and coma, and in many cases edema.

Intraperitoneal injection of bile from the gallbladder of dogs into nine dogs in amounts of 5 cc or more per kilogram of body weight caused death within twenty-four hours. Sterilized bile had the same effect as shown in the accompanying illustration.

## GENERAL COMMENT

The first series of experiments questioned the supposed relation of bile to peritonitis, and brought forward the question as to the combined action of bacteria and bile in the production of the peritonitis. Various authors have stated that bile was practically harmless when sterile, and attributed most of the serious cases to the infected contents of the gallbladder. One writer stated that almost all gallbladders containing stones are harboring bacteria which become virulent when free in the peritoneal cavity. But another writer stated that the bile is generally held to be antiseptic and antitoxic. If the latter were true there would be little need for the present elaborate care in the technic of operations on the gallbladder, and a perforation of the gallbladder or ducts should not cause worry.

Respiration

1 hr

Pt. Counted  
normal

1 hr

2 hr

3 hr

45 mins

30 mins

15 mins

Surv. Time

Dog 113 ♂ 6.2 kg  
April 8. 1927

Intra-peritoneal  
injection of  
31 cc. whole g. Bile

Lethal

Death

5 sec

Record of dog given ether-barbital anesthesia Intra-peritoneal injection of 31 cc of whole bile from the gallbladder, showing gradual failure of the heart and the blood pressure Death at the end of three hours

But when a permanent fistula was made between the gallbladder and the peritoneum, all the dogs died within twenty-four hours. Bacteria were found in only a few cases, and apparently had little if any effect on the course of the disease. The only conclusion that could be drawn was that more bile entered the peritoneal cavity by way of the fistula than when the gallbladder was merely opened, emptied and closed. In addition, ligation of the common duct precluded the possibility of bile passing into the intestines, and all these dogs died within twenty-four hours. It appears that when there is a lumen in the gallbladder wall, practically all the bile passes out into the peritoneal cavity, as there is not enough pressure in the ducts to cause passage of bile into the intestines along the normal pathway. The ligature also prevented the possibility of pancreatic juice passing out into the peritoneal cavity by way of the gallbladder and adding a complicating factor.

The whole question resolved itself into one of the quantity of bile in the gallbladder. Hence, bile was taken from the gallbladders of sixty-two dogs and measured, the largest amount obtained from one dog was 24 cc, this dog weighed 19 Kg. The smallest amount was 3 cc, the average was 8.1 cc, and the average weight of the dogs 9 Kg. Accordingly, when the gallbladder was merely opened, emptied and closed, an average of only 0.9 cc per kilogram of body weight got into the peritoneal cavity. When the lumen is left open, certainly a much larger quantity enters within a few hours. Bile from the gallbladder was then injected intraperitoneally in varying amounts up to 6 cc per kilogram of body weight and it was found that 5 cc per kilogram of body weight caused death within twenty-four hours. Sterilized bile had the same effect as unautoclaved bile.

*Clinical Symptoms and Signs of Bile Peritonitis in Dogs*—Rigidity of the abdominal muscles, especially in the right upper quadrant, and retching and vomiting occur, pain may be extremely severe, early defecation and later, watery or bloody stools occur, bradycardia, irregular heart, weak pulse, slow and irregular respiration, early restlessness, later, lethargy, and finally coma and death occur, urine, if obtainable, contains bile and albumin (usually total anuria), edema was present in 30 per cent of the dogs, jaundice was slight and sometimes questionable. Apparently the renal portal in dogs is low for bile pigments, as they are rapidly excreted in the urine.

#### TREATMENT OF BILE PERITONITIS

An attempt was made to treat animals with bile peritonitis by intravenous injections, with the idea that it might be possible to neutralize the action of bile salts as they came into the blood stream and thereby prevent them from injuring the heart, kidneys or other vital organs, and

to sustain the blood pressure and heart action. Epinephrine was also used (dogs 111 and 114) after a lethal dose of bile had been given, and it was found that epinephrine had only a temporary effect (from three to eight minutes), that the course of the disease was the same after the effect of the epinephrine, which was transitory, had passed and that the course was unmodified, death occurring at the same time as if epinephrine had not been used. It was hoped by this method to raise the blood pressure to such an extent that the kidneys would continue to excrete, thereby eliminating the toxic bile salts from the circulation. Ephedrine had a slightly prolonging effect, but the course of the disease was not modified.

The dilution of the bile and bile salts when injected intraperitoneally and also their dilution when injected intravenously were considered, so that a fairly weak solution would be injected, which would not take effect so rapidly. The use of sodium chloride with bile and bile salts in the intravenous injections appeared to give a slower rate of action, but if the total quantity of bile was injected within one hour, the toxic effect was the same as with the lesser dilute solutions.

The rate of injection markedly influences the toxic action of bile, as was demonstrated by Meltzer and Salant in 1906, but when a given amount of bile salts or of bile is injected within a period of one hour, even though it may be injected slowly, the apparent total effect is the same. Of course, if only a small quantity of bile is injected, less than a lethal dose per kilogram of body weight, for example, 2 cc, and injected as rapidly as it can be put into the blood stream, there may be immediate death. This occurred in dog 22, when whole bile was injected intravenously. The dog died immediately. Autopsy showed an immense thrombus extending even through the heart and into the lungs. This, of course, would mean an immediate massive destruction of blood cells, and the effect is not due to the toxicity of the bile so much as it is due to the mechanical effect of the thrombus. Accordingly after that all injections were made slowly enough to avoid the formation of thrombi. When bile is injected slowly, a formation of thrombus or a fatality from embolism rarely occurs. Bile, of course, lyses the blood but I have never had more than a 10 per cent laking of the blood, and this is not sufficient to give reaction from that alone. Serum containing 10 per cent hemoglobin from blood taken after intravenous injection of bile (dogs 123 and 118) was injected intravenously into dogs 125 and 119, respectively. It did not cause a reaction. Accordingly, I cannot agree with Meltzer and Salant that large quantities of bile can be injected without toxic effects if one places the limit of the injection of the bile or bile salts at the lethal dose within one hour, and that has been used as the standard.

*Chemical Methods of Abating Bile Peritonitis*—The literature contains frequent references to the effects obtained by injecting calcium, on the theory that calcium combines with bilirubin, making a hypocalcemia or diminishing the available calcium. A lethal dose of whole bile was injected intraperitoneally into dogs and calcium chloride, 10 per cent, given intravenously at various intervals, but the dogs died, as usual, in twenty-four hours. Because of the transitory nature of excess calcium in the blood and the exceedingly rapid action of bile in the blood, various intervals of time were used between the injection of calcium and bile in the blood, also, various quantities of calcium chloride were used, but the course of the disease was not affected. Calcium chloride was then mixed with whole bile before a lethal dose of bile was injected into the peritoneal cavity, and to my surprise the dogs lived only half as long as the average dog lived without the use of calcium chloride. Apparently, then, the action of calcium chloride was the exact reverse of what was expected. The experiment was repeated several times, and the results were the same in all cases, that is, there was not only no protective action, but the length of life was shortened by a half. The question then came up as to the toxicity of the calcium chloride which was injected. For a control, the same quantity of the same preparation of calcium chloride was injected into the peritoneal cavity, and toxic effects did not occur (table 1).

*Calcium Lactate*—Stewart and King stated that they rendered the bilirubin inactive by the use of calcium lactate. Calcium lactate was mixed with whole bile and the mixture injected intraperitoneally, and the dog lived for ninety-six hours. At autopsy, the abdomen was literally filled with adhesions and exudate, the most extensive that had yet been observed. To be sure, life was prolonged, but the marked tendency to adhesions would certainly be serious. The second dog received calcium lactate and bile intraperitoneally and died in twelve hours. Autopsy showed a large quantity of fluid in the peritoneal cavity—typical bile peritonitis. The control dog in which calcium lactate alone was injected lived for several weeks.

*Cholesterol and Lecithin*—Cholesterol and lecithin were considered because of their association with bile in the gallbladder. Pure cholesterol and lecithin were each mixed separately with whole bile and injected intravenously. The toxic effects were slightly diminished. When they were injected intraperitoneally, a modification in effects was not noticed. So apparently, then, the cholesterol and lecithin when injected with pure bile salts or with the bile itself modify the toxic effect only slightly.

*Fats*—In a recent article by Potter on the treatment of fistula following operation on the gallbladder, drains soaked in olive oil were advised. I had previously thought that perhaps the bile in the intestine is



physiologically rendered inactive by its early combination with fats. Accordingly, I used olive oil mixed with bile and bile salts for intraperitoneal injection, and in all cases found that the dogs died much sooner than they would have died without the use of olive oil. The

TABLE 1—*Intraperitoneal Injection of Whole Bile from the Gallbladder and Bile Substances\**

Dog	Weight, Kg	Material	Amount, Cc		Results
126	5.0	Bile	25	8 a m, calcium chloride, 10%, 5 cc, intravenously 3 p m, calcium chloride, 10%, 5 cc, intravenously 8 p m, calcium chloride, 10%, 5 cc, intravenously	Dead after 24 hours, typical bile peritonitis
127	2.0	Bile	10	Calcium chloride, 9 cc, intraperitoneally	Dead after 11 hours, intestinal contents bloody
128	6.0	Bile	30	Olive oil, 20 cc, intraperitoneally	Dead after 5 hours, bile peritonitis
129	3.7	Bile	18.5	Calcium lactate, 5%, 10 cc, intraperitoneally	Dead after 96 hours, many peritoneal adhesions, bile peritonitis
130	9.5	Bile	47	9 a m, physiologic sodium chloride, 200 cc, intraperitoneally 3 p m, physiologic sodium chloride, 200 cc, intraperitoneally 8 p m, physiologic sodium chloride, 200 cc, intraperitoneally	Condition remained good, living after 35 days
132	2.2	Bile	11	Olive oil, 4 cc, intraperitoneally	Dead after 7 hours, peritoneum pale
133	4.0	Bile	20	Calcium chloride, 10%, 10 cc, intraperitoneally	Dead after 6 hours peritoneum hyperemic, fluid
134	4.0	Bile	20	Calcium lactate, 5%, 20 cc, intraperitoneally	Dead after 12 hours, fluid in peritoneal cavity
135	5.2	Bile	31	4 p m, sodium chloride, 0.8%, 100 cc, intravenously 11 p m, sodium chloride, 0.8%, 100 cc, intravenously 8 a m sodium chloride, 0.8%, 100 cc, intravenously 2 p m, sodium chloride, 0.8%, 50 cc, intravenously	Dead after 5 days, adhesions throughout abdomen, fluid in abdomen, 200 cc
136	2.8	Bile	14	4.30 p m, sodium chloride, 0.8%, 100 cc, intraperitoneally 11 p m, sodium chloride, 0.8%, 100 cc, intraperitoneally 8 a m sodium chloride, 0.8%, 100 cc, intraperitoneally 3 p m sodium chloride, 0.8%, 50 cc, intraperitoneally	Dead after 6 days, no adhesions in abdomen, cause of death not determined
137	5.0			Calcium lactate, 5%, 20 cc, intraperitoneally	Dead after 8 days, pneumonia
138	5.2			Calcium chloride, 10%, 10 cc, intraperitoneally	Living after 20 days, well
139	7.0			Olive oil, 20 cc, intraperitoneally	Living after 20 days, well

\* Bile was mixed with various chemicals to test the inhibitory effects of such chemicals on the toxicity. Calcium chloride, calcium lactate and olive oil did not have an inhibitory power but even in most instances caused acceleration of the poisonous action of bile. Injections of these chemicals alone into control dogs did not cause toxic symptoms. Large quantities of sodium chloride solution given intravenously and especially intraperitoneally produced the most favorable results.

control dog in which olive oil alone was injected intraperitoneally was living twenty days later and was normal. The results suggested the theory that the fats rendered the bile salts much more rapidly absorbable, and instead of the immense amount of fluid being poured out into the

abdomen and the bile salts being absorbed at such a rate that they caused death within twenty-four hours, the bile salts with fat were absorbed so that death occurred within from five to seven hours

*Surgical Treatment of Bile Peritonitis*—In a number of dogs the gallbladder was opened and left open as in the early operations and after varying intervals of time, the abdomen was aseptically reopened and the gallbladder closed. Various intervals of time were set for the closing of the gallbladder, all of which must be within twenty-four hours. At the time the gallbladder was closed, the peritoneal cavity was thoroughly washed out with sodium chloride solution and a quantity of the solution was left in the peritoneal cavity. The dogs in which the second operation was done at eighteen hours all died, one lived at sixteen hours, all lived at twelve hours or less. Apparently, then, the maximum time at which the operation can be done following rupture of the gallbladder is sixteen hours, the preferable time is twelve hours or less. This, of course,

TABLE 2—*Typical Results of Operative Treatment of Bile Peritonitis\**

Dog	Operation	Treatment	Result
82	Laparotomy gallbladder was opened and left open, abdomen closed as in usual operation, aseptic technic	8 hours later the abdomen was reopened and the lumen in gallbladder closed, peritoneal cavity thoroughly washed out with 1,000 cc of sodium chloride, 0.8%, and 200 cc left in abdomen and the abdomen closed, aseptic technic	Lived
83	Same	12 hours later, the same procedure was followed as in dog 82	Lived
85	Same	18 hours later, the same procedure was followed as in dog 82	Died

\* Dogs that had a ruptured gallbladder with bile pouring out into the peritoneal cavity lived if they were operated on early, that is, within sixteen hours following the rupture, and the peritoneal cavity washed out with salt solution

presupposes the supposition that enough bile has entered the peritoneal cavity so that death will occur in twenty-four hours. In addition to the closing of the gallbladder and the washing of the peritoneal cavity, an intravenous injection of sodium chloride solution causes the animal to return to normal condition more rapidly, raising the blood pressure and increasing the activity of the kidneys. Water by mouth could not be used in these animals because of the persistent vomiting, neither can fluid be used by rectum because of the frequent diarrhea. The dogs always drink excessively when water is before them, but almost immediately vomit the entire contents of the stomach, so that little can be gained by attempting the intestinal route. Intravenous injection is preferable to hypodermoclysis (table 2)

#### CLINICAL APPLICATION

From a review of the literature in which the diagnosis of bile peritonitis has been made at autopsy or at operation, it seems that rupture of the gallbladder or biliary ducts is extremely serious—a mortality rate of

50 per cent or more. The cause of the high mortality would appear to be due in large part to the failure to make an early diagnosis and to recognize the seriousness of the condition. Such patients are usually seen by the family physician and the industrial surgeon. A delay of a few hours will cost the life of the patient.

The outstanding symptoms in experimental bile peritonitis are sudden spasticity of the abdominal muscles, nausea and vomiting, continuous pain, generalized in the abdomen, restlessness, early defecation, then diarrhea with bloody stools, and bilirubin in the urine. Later, the heart becomes slow and irregular, blood pressure falls, the respiration is slow or of the Cheyne-Stokes type, albumin and blood are found in the urine and coma occurs. When these late symptoms appear, the animal is in a precarious condition.

Chemical treatment, such as calcium chloride given intravenously and intraperitoneally, was of little if any value. Epinephrine and ephedrine sustained the heart temporarily, but this effect was transient. Salt solution given intravenously and subcutaneously did prolong life. Experimentally, it was found necessary to operate within the first sixteen hours, as the dogs did not live when operated on later than that. Practically all the dogs were saved when operation was performed prior to twelve hours after the rupture. The use of oils, calcium salts and cholesterol and lecithin in the peritoneal cavity was without value, and in some instances hastened the poisonous action of bile.

The treatment found to be the best was closing the opening in the gallbladder or bile passages, thorough lavage of the peritoneal cavity with warm physiologic sodium chloride solution, and then leaving a few hundred cubic centimeters of the salt solution in the abdomen followed by complete closure. With this, intravenous injection of salt solution was of value.

It is extremely important that a correct diagnosis be made within the first few hours following spontaneous or traumatic rupture of the biliary system, and that proper surgical treatment be instituted.

#### CONCLUSIONS

Bile from the gallbladder in the peritoneal cavity of dogs in amounts of 5 cc or more per kilogram of body weight causes peritonitis and death within twenty-four hours.

Bacteria are not essential and do not modify the course of bile peritonitis when bile is present in a sufficient quantity to cause death within twenty-four hours.

From this series of experiments, it seems that bile peritonitis is a clinical entity.

Calcium chloride and calcium lactate neither inhibit nor diminish the toxic action of bile

Olive oil accelerates the toxic action of bile

Cholesterol and lecithin slightly inhibit the toxicity of bile

Epinephrine and ephedrine have favorable effects, but the effects are exceedingly transient

Physiologic sodium chloride solution given intraperitoneally, intravenously or subcutaneously has the most favorable effect on the course of the disease

Early diagnosis and immediate operation are imperative

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# HYPERBILIRUBINEMIA IN PEPTIC ULCER \*

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Clinical jaundice is sometimes an accompaniment of duodenal ulcer when no other reason than the ulcer is apparent for its existence. Thus, it has been described as a symptom of duodenal ulcer by Reed,<sup>1</sup> Ewald,<sup>2</sup> Kemp,<sup>3</sup> Schmidt<sup>4</sup> and others. Usually it is described as a rare symptom<sup>5</sup> but Collin<sup>6</sup> found jaundice in nine of sixty-two cases of duodenal ulcer.

With the development of more exact methods of estimation of bilirubin in the blood, the question of possible jaundice in duodenal ulcer has become interesting. For, if clinical jaundice is present either as a rare symptom of ulcer or occurs in some series oftener than once in ten cases and, since the location of duodenal ulcer is fairly constant, it would seem possible that a certain proportion, possibly a large group, of patients with duodenal ulcer would show latent jaundice. If this is true, the interpretation of hyperbilirubinemia might be confusing unless duodenal ulcer had been carefully excluded. It has even been suggested<sup>7</sup> that duodenal and gastric ulcers might be differentiated by means of calculation of the icterus index.

Different and confusing reports of the bilirubin content of blood in patients with duodenal ulcer have been made. Bernheim<sup>7</sup> found the icterus index above normal in sixteen patients with duodenal ulcer, while twelve patients with gastric ulcer showed normal figures. In a series of thirty persons with ulcers, Scherck<sup>8</sup> found thirteen with distinct elevation of bilirubin, he used van den Beigh's method, measuring in bilirubin

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From the Third Medical Division of Bellevue Hospital.

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2 Ewald, C. A., in Billings, F. *Diseases of the Digestive System*, Modern Clinical Medicine, New York, D. Appleton & Company, 1906, p. 199.

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5 Reed (footnote 1). Kemp (footnote 3).

6 Collin, quoted by Scherck. *Arch. f. Verdauungskr.* **37** 344, 1926.

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8 Scherck, K. *Ueber die differential diagnostische Bedeutung des Bilirubin-spiegels im Blut bei Magen- und Gallenblasenaffektionen*, *Arch. f. Verdauungskr.* **37** 344, 1926.

units and taking 1 as a high normal limit. He found the blood bilirubin above normal in seven patients with duodenal, in three with pyloric and in three with gastric ulcers. The highest reading of the duodenal series was 3 and the average of the abnormal readings, 1.84— Of the six persons with pyloric ulcers, three showed a bilirubin content above normal, with an average of 1.28 for the three. Of ten patients with gastric ulcers, the bilirubin in three was above 1, with an average of 1.25— Speik, Liljedahl and Falk<sup>9</sup> reported that hyperbilirubinemia was present in sixteen patients with duodenal and gastric ulcers. They used the Fouchet test. They stated that there was no evidence of disease of the gallbladder in these cases, but did not state what means were used to exclude such possibilities. This test was positive in one patient with bronchial asthma, two with angina pectoris, four with pulmonary tuberculosis and others. Haak<sup>10</sup> thought that some persons with duodenal ulcers give high blood bilirubin calculations. He saw five such cases. On the other hand Friedman and Strauss<sup>11</sup> found that four patients with gastric and six with duodenal ulcers did not show hyperbilirubinemia. They concluded that the presence of hyperbilirubinemia is of value in deciding between cholecystitis and gastric and duodenal ulcer or carcinoma. Arnoldi and Schechter<sup>12</sup> estimated the bilirubin of the blood in persons with secretory disturbances of the stomach. They found it low normal in those with hyperacidity and high normal in those with lowered acidity and achlorhydria.

It has been suggested by Barrow, Armstrong and Olds<sup>13</sup> that adhesions about the duodenum block the ducts and cause the jaundice. Other explanations have included swelling<sup>8</sup> near the papilla of Vater with mechanical obstruction and a vagotonic state<sup>8</sup> resulting from the ulcer, with reflex spasm of the ducts.

In the papers already mentioned, when hyperbilirubinemia was found in patients with duodenal or gastric ulcer, mention was not made of the steps taken to exclude other abdominal disease. Thinking that this might be a source of disagreement, we have selected from cases occurring in the wards of the Third Medical Division of Bellevue Hospital and the Clinic of Gastro-Enterology of New York University ten

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9 Speik, F. A., Liljedahl, E. N., and Falk, M. A. Observations on the Fouchet Test in Latent Jaundice, *J. A. M. A.* **82** 2092 (June 28) 1924.

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patients with gastric and thirteen with duodenal ulcer, in whom roentgen-ray study, physical examination and history exclude disease of the gallbladder and gall duct and periduodenal adhesions as far as possible. Blood serum was collected from these twenty-three patients and the direct van den Bergh and the quantitative indirect tests and determinations of the icterus index were made.

The technic for the icterus index was that of Meulengracht, as modified by Gram and by Bernhard and Mane and as given by Beinheim.<sup>7</sup> The method for the van den Bergh reaction as given by McNee<sup>14</sup> was followed carefully.

The results of this study are given in the accompanying table.

*Results of Study of Twenty-Three Patients with Ulcers*

Location of Ulcer	Direct	Indirect Units	Color Index
Stomach	Negative	0.1	
Stomach	Negative	0.5	4
Duodenum	Negative	0.6	5
Duodenum	Negative	0.5	4
Duodenum	Negative	0.6	5
Duodenum	Negative	0.4	3
Duodenum	Negative	0.9	6
Stomach	Negative	0.4	3
Stomach	Negative	0.4	3
Stomach	Negative	0.4	3
Duodenum	Negative	0.3	3
Pylorus	Negative	0.5	4
Duodenum	Negative	0.4	3
Duodenum	Negative	0.4	3
Pylorus	Negative	0.4	3
Duodenum	Negative	0.3	2
Stomach	Negative	0.75	5
Stomach	Negative	0.5	4
Duodenum	Negative	0.3	2
Duodenum	Negative	0.3	2
Duodenum	Negative	0.6	4
Duodenum	Negative	0.4	3
Stomach	Negative	0.5	4

#### SUMMARY AND CONCLUSIONS

Conflicting reports as to the occurrence of latent and actual jaundice in persons with duodenal ulcer led us to investigate twenty-three cases of duodenal and gastric ulcer in which roentgen-ray and other examination did not reveal evidence of a pathologic condition of the gallbladder or gall duct or adhesions in the upper part of the abdomen. Determinations of bilirubin in the blood serum of these patients showed a normal amount in every instance. This confirms the observations, in the smaller series, of Friedman and Strauss. These results would tend to support the suggestion that jaundice when present in persons with duodenal ulcer is either caused by periduodenal adhesions, catarrhal inflammation of the duodenum or a complication in the biliary system.

14 McNee, J. W. Jaundice, Review of Recent Work, *Quart J Med* 16: 390 (July) 1923.



# CLINICAL SPIROGRAPHY

## SPIROGRAMS AND THEIR SIGNIFICANCE\*

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AND

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Since 1923, all determinations of the basal metabolic rate conducted in the Battle Creek Sanitarium Clinic have been made by the graphic method. These graphs form the subject of our present study. We have chosen to call them spiograms to differentiate them from the numerous other types of graphs used in medicine.

While a casual observation of these tracings gives the impression that every conceivable irregularity may be obtained, a closer inspection reveals that there is a certain order in the apparent chaos. One of us (P. R.) first noted that the spiograms could be divided into about ten types, each with definite characteristics. For the past four years all spiograms have thus been read and classified on a purely graphic basis by one technician. We take pains to state that the reader of the spiograms had not the slightest idea whether they had any clinical significance, but was interested only in accurate observation of the tracings. Prejudice or bias based on unconscious clinical observation, therefore, cannot play a rôle in the classification.

When about 20,000 tests had been made, we undertook to determine what the significance of these spiograms might be. Unexpected and valuable data have been discovered. The diagrams with original instructions as given to the technician are reproduced in figure 1.

A normal pneumogram has been described repeatedly and is recognized in standard physiology. A spiogram obtained by the usual graphic metabolism apparatus is practically identical with this. The pen ascends with each inspiration. The depth of inspiration varies considerably more than the depth of expiration, because expiration is a passive act. A line drawn, or imagined drawn, to connect the inspiration apexes is called the inspiratory line. This is the upper margin of the tracing. A similar lower margin gives the expiratory line. (The geometrical line drawn close to the lower margin is entered by a technician for purposes of calculating the basal metabolic rate and has

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\* From the Research Department of the Battle Creek Sanitarium Clinic.

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nothing to do with typing the tracing) A normal tracing has a regular and even expiratory line and a slightly irregular inspiratory line There is a slight pause at the end of each expiration

Type *A* is almost identical with a normal respiration It is characterized by a fairly regular inspiratory (upper) line and a regular expiratory (lower) line In addition, there is a slight pause at the end of each expiration There are two subtypes (*A* and *A*<sub>2</sub>), the second showing more irregularity than the first

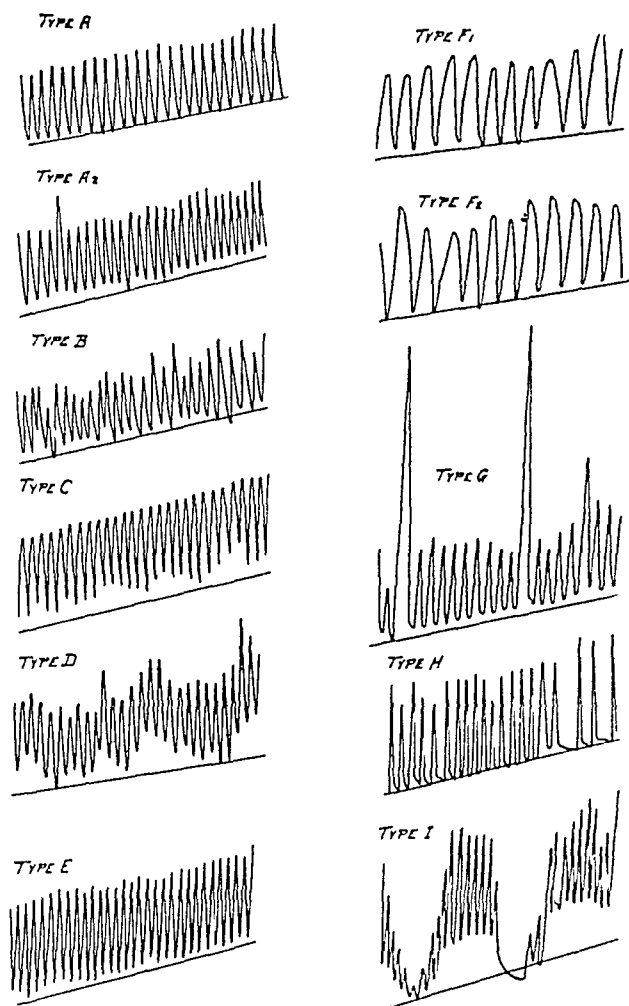


Fig 1—Diagrammatic illustration of the nine respiratory types here presented In type *H* the tracing is not long enough to show the waviness referred to in the description See figure 3

Type *B* is determined by an irregular irregularity of the inspiratory and expiratory lines, especially the former, otherwise it is like the irregular type *A* (*A*<sub>2</sub>)

Type *C* is an inverted type The inspiratory line is practically straight, while the expiratory line is somewhat irregular The slight pause in each respiration occurs at the end of inspiration instead of at expiration

Type *D* shows a periodic and fairly regular wavy contour in both inspiratory and expiratory lines—a ribbon-like formation. The regularity distinguishes it from type *B*.

Type *E* presents a normal general contour, but in the individual respirations there is no pause either at inspiration or at expiration.

Type *F* is characterized by a normal general contour, but there is a definite pause at inspiration. In this sense it is a reversal of the normal.

Type *G* has the normal inspiratory line interrupted by frequent and extremely deep inspirations. The intermediate portions of the tracing are normal.

Type *H* shows a definite regular waviness in the inspiratory line. In addition, there is a pronounced pause at each expiration.

Type *I* is the well known Cheyne-Stokes type. There is a periodicity in the entire contour, a tendency to crescendo and diminuendo in the individual respirations and a pause at expiration considerably greater than that encountered in type *H*.

It is not feasible in this brief paper to give the data or all of the reasoning that led up to our conclusions. This will have to appear in detail elsewhere. We shall merely state briefly the general method of procedure.

Two approaches were used in order to avoid the errors likely to creep into a statistical study. The first was the approach from types to clinical observations, the second from clinical observations to types. In other words we selected first all the cases of one type and determined their characteristics, then we selected all cases of one characteristic and determined in which types they occurred. The cases were divided into constant and inconstant, according to whether the same type of respiration was manifested in every test or whether different types occurred in the various tests.

#### CHARACTERISTICS OF THE TYPES STUDIED

To determine the characteristics of the types, only the constant cases were used. These were studied from the standpoints of age, race, sex, state of nutrition, basal metabolic rate, pulse rate, respiration rate; results of urinalyses, acidity, sugar, albumin, acetone, casts and blood cells, observations on the blood cell count, hemoglobin content by the Dare method, Wassermann test, nonprotein nitrogen, uric acid and sugar content, alveolar carbon dioxide tension and acetone, ventilation of the lung in liters per minute, and all diagnoses. The incidence of every item was first determined on the normal series, and this was used as a control. Unless a condition occurred in any type to such a degree that

it differed from the normal by one-third, it was not admitted as an established abnormality

A study of the inconstant cases was productive. There were two types of inconstancy, one in which a tracing partook simultaneously of the characteristics of two typical spiograms and cases which fell in one type in one test and in other types subsequently. This gave us a good insight into the type interrelationships. We found that there was a definite association between certain types and apparently an impossibility of association between others. Only twelve of thirty-six theoretical possibilities actually occurred (fig 2). The most striking feature of figure 2 is the fact that it shows that a patient with a normal

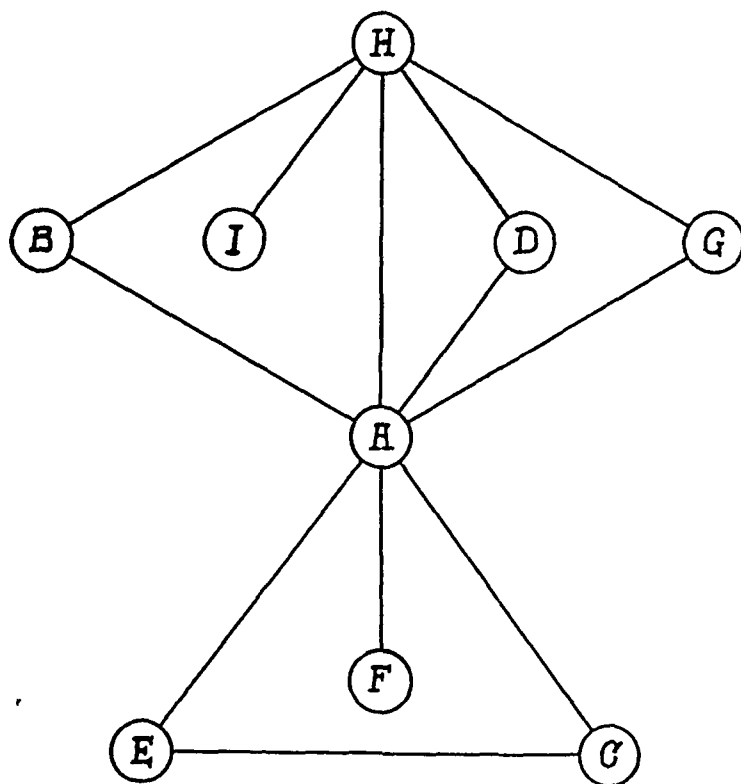


Fig 2—Diagram to show type interrelationships. The central situation of type *A* and its connections with all types except *I* can be noted. Types *F* and *I* each have only one relationship.

respiration cannot possibly develop a Cheyne-Stokes type (*I*) unless he first develops type *H*.

The clinical characteristics of the various types as determined by this work are as follows:

Type *A* is the normal and serves as the control. It may be the precursor of others when sufficient cause arises to alter the type. It is related to all other types except *I*. There is hardly a disease process incompatible with a normal type of respiration, but other factors e.g., puberty or chemical changes of the blood, may incite to bring about a change.

Type *B* may arise by a dynamic process in the endocrine system. Its most common associations are with types *A* and *H*. Conditions which occur in this type considerably oftener than in the normal type are hypotension, neurotic and psychotic states, mucous colitis and endocrine disturbances. Type *C* occurs practically exclusively in women, and hence we believe that it is controlled by some unusual function of the female hormone. We are not in a position to make any other statement concerning it, because of the paucity of our material.

Type *D* is largely, though not exclusively, masculine (about 88 per cent). It occurs in young boys as early as they can be tested (before puberty). In this type there is a peculiar mixture, a tendency to endocrine disturbances with both hyperthyroidism and hypothyroidism, and also a tendency to cardiovascular-renal disease. This is manifested by

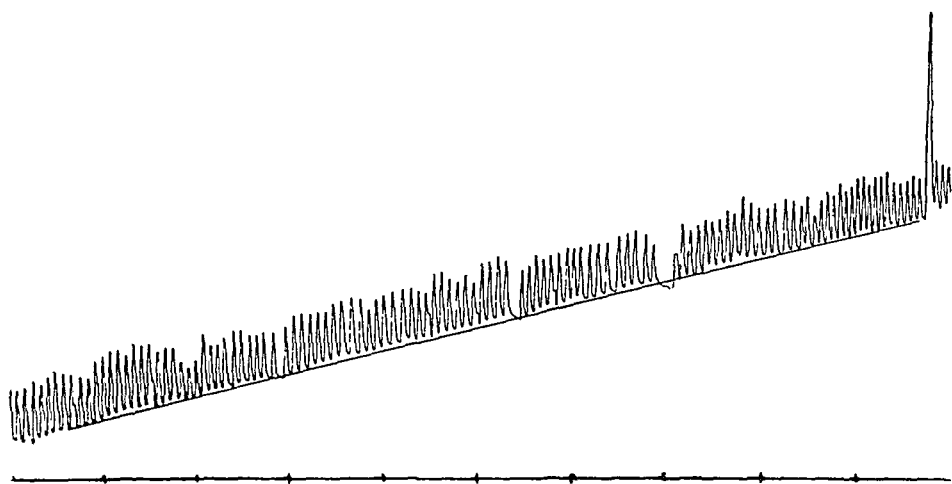


Fig 3—Spirogram illustrating the wavy appearance of the inspiratory line and the exaggerated pause at the end of expiration, which are the characteristics of type *H*.

the retention in the blood of nonprotein nitrogen, uric acid and sugar. Osteo-arthritis and obesity also are prevalent in this type, while neurotic and psychotic manifestations and constipation are rare. The associations are with types *A* and *H*.

Type *E* though graphically appearing entirely different from the former is nevertheless somewhat similar clinically. It resembles type *D* in retention of nonprotein nitrogen, uric acid and sugar in the blood and in the occurrence of osteo-arthritis. But it differs from *D* in prevalence of colitis and neurotic states and in the absence of endocrine disturbances. Its associations are with types *A* and *C*.

Type *F* is one of the rare types and has only one association with the normal. There is a low nonprotein nitrogen content in the blood, and obesity is prevalent.

Type *G* is an important type, occurring practically exclusively in the female. It develops in certain girls at puberty. Once established it does not disappear at menopause. Hypertension, myocarditis, obesity and osteoarthritis prevail. Endocrine disturbances are common.

Type *H*, the suggestive Cheyne-Stokes type, occurs in childhood but also develops from type *A* with which it is closely related. It is the inevitable precursor of type *I*. A high uric acid content of the blood and myocarditis occur in this type. Its associations with types *A*, *B*, *D*, *G* and *I* are numerous.

Type *I* is the typical Cheyne-Stokes type and develops from type *H* under certain conditions, among which is a high uric acid content in the blood. This type is seldom seen in a woman. It rarely occurs before the age of 50. While the patients in the majority of the cases in this type have cardiovascular renal disease or diabetes, there are some who develop it without suffering with either of the diseases mentioned, however, they all have an increase in uric acid.

At this point the question of necessity arises whether the respiratory types on the whole are caused by these abnormal physical states. As practically all disease processes occur in the presence of a normal type, serious doubt is cast on this point. It occurred to us that this question might be solved by studying respiratory types in children, making use of our patients as early in life as they could be tested. This line of research proved extremely valuable because it was found that types *A*, *B*, *D*, *E*, *F* and *H* may all occur in childhood. In fact we are forced to conclude that the types named are probably evidence of hereditary characteristics—perhaps an hereditary condition of the respiratory center. If this is the case, the preponderance of certain diseases in the types must be merely an associated condition.

To either confirm or deny the concept that the types are largely hereditary, a special study of this point was made. Three families were obtained in which the parents and at least four children could be tested. In each of two families five children were obtained, in the third, there were only four. A definite inheritance was shown.

#### CONCLUSIONS

- 1 All persons can be divided purely on the basis of their spiograms into about nine types which we have lettered. (A few extremely rare types are still to be studied.)

- 2 Respiratory types *A*, *B*, *D*, *E*, *F* and *H* are hereditary, and the occurrence of these types merely presages certain predispositions in the person.

- 3 Types *C* and *G* are controlled by some unusual function or influence of the female hormones.

4 Types *D* and *I* are similarly but to a more limited extent controlled by the male hormones

5 Certain individual characteristics and disease processes are shown by this work to be of an hereditary nature. Namely, (1) cardiovascular renal disease, (2) nonulcerative colitis, (3) increased blood sugar, uric acid and nonprotein nitrogen content, (4) endocrine instability in general and specifically hyperthyroidism and hypothyroidism, (5) hypotension, (6) myocarditis, (7) nervous and mental states, (8) obesity and (9) osteo-arthritis

6 As the hereditary predispositions to certain diseases can be determined in early childhood, the application of this work to preventive medicine is obvious

# ALBUMINURIA IN THE MECHANISM OF DETOXIFICATION

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It is our purpose in this paper to present data indicating that the presence of serum proteins in the urine in nephritis is due to their combination with other nitrogenous fractions of tissue origin, some of which are highly toxic. It is our belief that this combination acts as a detoxicating mechanism and that the elimination of this protein by the kidneys is due to alteration of normal serum proteins by their combination with other split protein products which render them foreign to the circulation.

It has been apparent for some time that the renal element in nephritis is relatively unimportant and that theories of nephritis based solely on renal damage must be abandoned. The Aldrich and McClure<sup>1</sup> intradermal salt test as well as the series of experimental dehydrations reported by one of us<sup>2</sup> gives ample evidence that Martin Fischer was right in ascribing edema to a greater colloid affinity of the tissues for water, and that anuria may result from this factor alone. Experimental renal damage and partial or total nephrectomy do not produce the clinical picture of uremia, and clinically such cases are frequently reported with normal nonprotein nitrogen values in the blood. Similarly enormous high nitrogen levels have been found in the blood without uremic symptoms.

In a previous communication<sup>3</sup> this theory was elaborated, and the complete picture of uremia was reproduced by simply disturbing the mineral salt balance. Profound changes in the calcium-potassium ratio were reported, and it was suggested that under uremic conditions the

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<sup>1</sup> Submitted for publication, Aug 18, 1928

<sup>2</sup> From the Department of Surgery and Physiological Chemistry of the University of Illinois School of Medicine

1 Aldrich, C A, and McClure, W B. Time Required for the Disappearance of Intradermally Injected Salt Solution, *J A M A* **86** 293 (July 28) 1924  
Aldrich, C A. The Clinical Course of Generalized Edema, *ibid* **84** 481 (Feb 14) 1925

2 Andrews, Edmund. Water Metabolism I, *Arch Int Med* **37** 82 (Jan) 1926, Water Metabolism II, *ibid* **37** 559 (April) 1926

3 Andrews, Edmund. Experimental Uremia, *Arch Int Med* **40** 548 (Oct) 1927



tissue permeability was increased to such an extent that products which were normally intracellular leaked into the blood. Later, tissue proteins were isolated from the urine in the early stages of both experimental and human nephritides, these proteins being recognized by precipitin reactions.<sup>4</sup> It is well known that most foreign proteins such as egg albumin or foreign serums injected parenterally will be excreted by the kidneys. Further work<sup>5</sup> confirmed our views that if tissue protein (liver) makes its way into the blood stream it will also pass through the kidneys just as a foreign protein will. A liver extract (containing, of course, both serum and liver proteins) injected intravenously into a normal animal will result in the passage of protein in the urine which is in a high degree specific to antiliver serums and does not react, even undiluted, with antiblood serums.

Pharmacologic studies of pure liver protein prepared by this means have shown that it is practically nontoxic and, therefore, is not the cause of clinical symptoms in nephritis. Former work has demonstrated unquestionably that the lower nitrogenous products are not the exciting cause of uremic symptoms, and it was predicted that substances of the proteose-peptone group would be identified as the offending agents.

This concept of nephritis, however, has signally failed to explain the mechanism of albuminuria. The proteins of the urine in nephritis are largely blood serum proteins, and the great stumbling block to the abandonment of older ideas of renal pathologic changes being fundamental was the question, why do apparently normal blood proteins pass through the kidney?

#### EXPERIMENTS

Studies of urinary proteins by precipitin reactions have at times yielded hitherto inexplicable results. In the usual process of purifying urinary proteins, they were saturated with ammonium sulphate up to the point where precipitation began (somewhere between 25 and 50 per cent saturation). The material is then set aside for crystallization. The first crop of crystals reacted in high dilution with antiblood serums. The second crop gave a much lower precipitin titer, and later crops failed almost entirely to react with antiblood serums. However, if the last crop which was not active with antiblood serums was injected into the rabbits, it produced an antiblood albumin blood serum of great strength. These experiments were tentatively interpreted as indicating that some substances had been in combination with the albumin which was broken off in the process of crystallization.

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4 Andrews, Edmund, and Thomas, W. A. The Origin of Urinary Proteins, *J. A. M. A.* **90** 539 (Feb. 18) 1928.

5 MacDonald, R. F., Thomas, W. A., and Andrews, Edmund. *Proc. Soc. Exper. Biol. & Med.* **25** 246 1928.

The next step was the recognition by methods of dialysis recently published<sup>6</sup> that there was a change in the character of the serum protein in nephritis. Small amounts of serum were placed in tubes, the end of which was closed with collodion membrane and placed in hundredth normal hydrochloric acid. Nephritic serums took on large amounts of water, the normal serums practically none at all. Careful chemical studies of these serums have ruled out chlorides, nitrogenous production of the urea group, acidosis and other factors, except the proteins themselves, as being the cause of this phenomenon. Although the nephritic serums contained much less protein than normal serums, their hydrophilic properties were far greater.

The last two groups of experiments suggested that there was some change in the proteins in the blood and the urine, and that the urinary proteins were not simply unchanged blood proteins. With these points in view, we studied the mother liquor in the crystallization experiments already described and found that it contained large amounts of peptone. As much as 4 Gm of peptone was recovered from a single batch of 18 liters of urine. A large number of further experiments yielded similar results. Again, if a solution of the precipitate of 50 per cent saturation with ammonium sulphate is dialyzed, peptone may be recognized in the dialysate. In the concentration of the dialysates, care must be taken to stop short of dryness in order to avoid increasing the coloring matter which will obscure results in both the biuret and the xanthoproteic tests.

This peptone was injected into dogs in varying amounts and was shown to be nontoxic. Two grams injected daily failed to produce any symptoms. In order to bring about even a transient albuminuria, a dose of 5 Gm intravenously was needed. Six grams was the lethal dose. This fraction, then, did not represent the toxic element, and further studies of dialysates were made. It was found that these dialysates contained a highly toxic protein. This protein is coagulable by heat. It reacts strongly with antiblood albumin and antieuglobulin serums. It does not react with antifibrinogen serums. However, its state of dispersion has been so changed, possibly by combination with some toxic factor, that it will readily pass through a collodion membrane. There is another possibility to be considered, *i. e.*, that the protein itself is toxic simply by virtue of its greater dispersion. Intravenous injection of 50 mg of this protein into dogs will produce deep coma and death in from twenty-four to forty-eight hours. In the early stages of the coma, the dog will twitch violently if touched. Later, the coma is so deep that he cannot be aroused by any means.

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6 Thomas, W. A., and Andrews, Edmund. A New Clinical Test for Tissue Thirst, *Proc Soc Exper Biol & Med* **25** 773 (June) 1928.

Similar results may be obtained with uremic serums. The dialysate of such serums contains a small amount of protein of the peptone proteose group, in our experiments, about 100 cc of uremic serum has been necessary to provide enough proteins to give recognizable reactions in the concentrated dialysate. The dialysis is carried on for only twelve hours, as in longer periods there is a possibility of hydrolysis of the serum protein. Control experiments on normal serums fail to show this phenomena. The amount of dialyzable protein recovered from human serums has thus far been too small to identify.

Urinary proteins of the dog have been studied, it was found that after crystallization and prolonged dialysis, those proteins did not produce toxic symptoms when injected intravenously into dogs, but if the same urinary proteins are subjected to dialysis for only a few hours to rid them of the more readily fusible urinary substances, they are toxic and will produce convulsions, coma and albuminuria, if injected intravenously.

#### COMMENT

From the foregoing data, the following hypothesis is offered as a tentative suggestion of the mechanism in uremia and nephritis.

Changes in the osmotic equilibrium are brought about. These are associated with alterations in the mineral salt balance which produce a markedly increased tissue permeability. This allows leakage into the blood stream, first, of normal tissue proteins, which are ordinarily retained within cell membranes. As these proteins are foreign to the circulation, they are excreted by the kidneys. Later, there follows a leakage into the circulation of other split protein products, certain of which are highly toxic and produce the symptoms of uremia. These substances are combined with the proteins of the blood or absorbed by them. This protein complex seems to have a smaller molecular aggregate or to be in a higher state of dispersion so that not only will it pass through the kidneys but part of it will even pass through a collodion membrane. The peptone itself is at least not free because if the serum protein is precipitated by heat or by saturation by ammonium sulphate, the peptone is precipitated with it, in crystallization or to a small extent by dialysis, it is freed from the larger albumin molecule and may then be identified, the protein bearing the toxic substances or which is toxic by reason of its higher state of dispersion passes readily through a collodion membrane, and if dialysis is continued for four or five days, the water being changed daily, subsequent dialysis yields a dialysate that reacts negatively to the biuret test.

Albuminuria may then be looked on as a protective mechanism on the part of the body to carry poisons from the seat of origin to the outside by the well known mechanism of neutralization by combination with

innocuous substances. These substances may represent normal stages in nitrogen metabolism, and the pathologic factor lies in their making their way into the blood stream, as already suggested. Another interesting possibility to be considered is that nephritis is comparable to diabetes in the sense that protein metabolism is interfered with by some means, so that oxidation is incomplete and the process stops at a state where the products of nitrogenous metabolism are toxic and are eliminated by the mechanism previously described.

#### CONCLUSION

- 1 The urine of nephritic persons contains, besides the normal blood proteins, a relatively nontoxic peptone combined or adsorbed by serum proteins and also a highly toxic blood protein so highly dispersed in solution as to pass readily through a collodion membrane.

- 2 The hypothesis is presented that albuminuria is a detoxicating mechanism for eliminating poisonous products of protein metabolism.

## Book Reviews

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**NURSES, PATIENTS AND POCKETBOOKS** A Report of the Study of the Economics of Nursing, Conducted by the Committee on the Grading of Nursing Schools  
By MAY AYRES BURGESS, Directress Price, \$2 1928

This is a report on a nation-wide study of supply and demand in nursing service. It is in a sense a preliminary report in a projected five years' study of the nursing situation by a committee of twenty-one members, fourteen of whom are officially appointed by the national organizations and seven elected as members-at-large. This is a fact-finding committee organized for the purpose of grading training schools.

The first part of the volume is devoted to information on the economics of nursing, the second part to an analysis of this information.

It was the original intent of the committee to first take up the grading of training schools, but it was later decided to study the supply and demand for nurses. This study reveals a marked oversupply in the face of a rapidly increasing number of graduates. They estimate that 17,500 graduated in 1926, compared with 3,456 in 1900. The training schools during this period increased from 432 to 2,155. During this time the number of nurses per hundred thousand of population has increased from 16 to 141, while the number of physicians has decreased from 173 to 137.

Registers, especially from large cities, indicate that the supply is equal to the demand with prospects of an oversupply in the immediate future. Public health organizations have more applicants than positions.

In addition to the topics mentioned, many other subjects are studied in detail, an effort being made to supply statistical data. This book furnishes valuable information to all those interested in nursing. When the work is completed and further volumes are published, a splendid reference work on the nursing problem will be available.

**A TEXTBOOK OF ACTINOTHERAPY** By D. D. ROSENWARNE, M. R. C. S., (England), L. R. C. P. (London) Price, \$4 Pp 237, with 20 illustrations, including a colored plate. St. Louis: C. V. Mosby Company, 1928.

The first sixty-two pages are taken up with fundamental physical and electrical facts, such as are given in a course of high school physics. The biologic action of light is discussed on pages from 73 to 103. Pages from 113 to 226 are devoted to clinical procedures, with a great deal of emphasis on autointoxication and colonic flushing. On pages from 143 to 176 diseases of the skin are dealt with, largely from the standpoint of light therapy.

The text is verbose, arrangement is often illogical and undue repetition is apparent. It contains many glaring errors, such as "Seborrheic Eczema—Affection of the sudoriferous glands," and "Sycosis, Eczema of the Hair Follicles." In the discussion of psoriasis, the author states "X-rays combined with ultraviolet radiations are probably the best treatment."

One gathers that cutaneous hyperpigmentation following actinotherapy is produced by the short light waves acting on nerve plexuses and affecting the sympathetic nerves. This evidently acts on the suprarenal glands, as later "The production of pigments by the adrenals under the influence of light." On the contrary, it has been shown repeatedly that the oxidase of the pigment-producing cell is increased. There is no method for demonstrating the melanogen.

The author complicates the application of actinotherapy, probably more so than is indicated by the present day knowledge.

The text contains some valuable material, but numerous errors tend to destroy one's confidence, and reduce its value.

The illustrations are excellent, and a bibliography is appended.

A TEXT-BOOK OF INFECTIOUS DISEASES By GOODALL and WASHBOURN  
Revised and in large part rewritten by E W GOODALL, OBE, MD, BS  
Third edition Price, \$10 Pp 709, with 26 plates, 9 other photographs, 15  
diagrams and 34 charts New York William Wood & Company, 1928

In bringing up-to-date his "Manual," the author has expanded it into a good sized textbook. He has added an introductory chapter on epidemiology which should prove interesting and stimulating to all students of infectious diseases. It fails, however, to cover the field as adequately as even such a brief and general discussion may reasonably be expected to do. The more recent work of Webster on experimental epidemiology may be cited as an example of a pertinent omission.

The clinical symptoms and signs of the various diseases are well described, the methods of treatment are up-to-date. But the presentation of the facts and theories concerning etiology leaves something to be desired. The problem of etiology is, in the case of several diseases, admittedly a vexatious one, and the author in his preface warns the reader that he is not a bacteriologist. Nevertheless, he cannot be unconditionally pardoned for his failure to mention, for instance, the studies of Dochez on scarlet fever, or those of the several workers who believe that measles is caused by a filterable virus.

The book is well printed and bound and contains numerous photographs, diagrams and fever charts, all of which should be highly instructive to students and practitioners.

SPECIAL CYTOLOGY Edited by EDMUND V COWDRY Two Volumes Price, \$20  
Pp 1,300 New York Paul B Hoeber, Inc

The two volumes comprising this work are made up of thirty-five sections by as many authors, covering the various special cells of the body. Each of the sections is largely monographic in character, since the writers have all made extensive contributions to the subjects with which they are dealing. The result is a work of the highest value which is unique in nature. Here within the scope of 1,300 pages is contained all the most important knowledge of the structure and function of the body cells. The introductory chapter indicates the new directions which research in cell function will probably take and mentions some of the possibilities of the more newly developed methods of study in this field. The different systems of cells, the skin and its derivatives, the respiratory tract, digestive tract, etc., are then taken up in an interesting and scholarly way. In addition to the anatomy and functional activity of the individual or group of cells, the organization of the cells into specific tissues as well as the embryologic and comparative anatomic aspects are discussed. In certain sections the general reactions of cells to disease agents and the changes occurring in pathologic states are touched on, but the subject matter does not include pathologic histology as might perhaps be inferred from the subtitle. This not only is a textbook for students of biology and medicine but is also an invaluable reference work for those engaged in special problems of cell biology. The book is beautifully printed. The illustrations are abundant and well executed, and each section is followed by an extensive bibliography.

CLINICAL STUDIES ON INFECTIONS OF THE URINARY PASSAGES IN CHILDREN  
(DANISH) By DR ARNE JOHANNESSEN Pp 350 Copenhagen Levin &  
Munksgaard, 1926

This is also a thesis for the MD degree done in the Pediatrics Department of the University of Copenhagen, under the direction of Dr Bloch. The second half of the monograph contains brief case records and histories of more than 100 patients investigated. The monograph is interesting as an illustration of the type of consecutive work and grasp of the literature in one field required for the MD degree in Denmark. Otherwise the study cannot be said to advance particularly the problem under investigation. The author concludes (on page 137)

that hematogenous origin of cystitis is most prevalent during the first year of life and that after the second year the entrance of bacteria through the external passages is assuming a more important rôle

**SYSTEMIC INFECTIONS THEIR DIAGNOSIS AND TREATMENT** By A KNYVETT GORDON, M B, B C, B A Cantab, Medical Superintendent of the Virological Pathological Research Laboratories, Consulting Pathologist to the Great Western Railway Medical Fund Society and to the Victoria Hospital, Swindon Price, \$4 New York William Wood & Company, 1928

According to the preface this book is intended primarily for those engaged in general practice But, in the opinion of the reviewer, the book can be read with profit only by the most poorly trained physician or by one who has completely forgotten the technic of thorough examination of patients and of the commonest laboratory procedures Chapters are devoted to elementary bacteriology and hematology, and a large portion of the book to the methods of searching for a focus of infection and of the treatment thereof

**PSYCHONEUROSEN FUNKTIONELLE NEUROSEN ERSCHÖPFUNGSZUSTÄNDE VON DR. WALDEMAR UNGER.** Praktische Differentialdiagnostik Band II, Neurologie Teil 2 Price, 8 marks Mit 3 Abbildungen Dresden und Leipzig Verlag von Theodor Steinkopff, 1927

The book is of special advantage to the general practitioner facing the problems of diagnosis and therapy of functional disturbances of the psyche The author surveys in a systematic manner the clinical pictures of exhaustions, constitutional disturbances, organic neuroses, hysteria, compulsion-neuroses, psychopathic personalities, migraine, epilepsy and combined pictures He then describes precisely diagnosis according to the most important clinical features The value of this study lies in general in the attempt of the author to do justice to the variety of syndromes, not forgetting the individual in favor of a preconceived idea of a psychopathologic unit.

**KLINISKE STUDIEN OVER URINVEJSINFEKTIONER HOS BØRN** By ARNE JOHANNESSEN Pp 350 Copenhagen Levin & Munksgaard, 1926

This manuscript is a thesis for a doctor's degree There are 100 complete case histories of pyelitis included, with excellent references, but no new ideas are advanced as to treatment The Norgaard pyometer is used to determine the amount of pus in the urine, as this method is more accurate than the microscopic estimation

**BIDRAG TIL STUDIET AF ASTHMA SAERLIG HOS BØRN** By KAJ BAAGOE Pp 284 Copenhagen Levin & Munksgaard, 1926

This is a thesis for a doctor's degree It contains 232 instructive case histories with excellent references There are not, however, any new ideas expressed on the subject

**CONTRIBUTION TO THE STUDY OF ASTHMA ESPECIALLY IN CHILDREN (DANISH)** By DR KAJ BAAGOE Pp 284 Copenhagen Levin & Munksgaard, 1926

This is a clinical study done under the direction of Dr Bloch, and the monograph is presented as a thesis for the M D degree The work embraced a study of between 200 and 300 patients The literature is presented and discussed ably and critically, but there is nothing essentially new in either the facts or the theory presented

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## CAN THE GALLBLADDER EMPTY THROUGH DUODENAL BILIARY DRAINAGE? IS THE GALLBLADDER THE SOURCE OF "B" BILE?

A CHOLECYSTOGRAPHIC STUDY OF BILIARY DRAINAGE \*

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PHILADELPHIA

In the discussion that followed a program on the diagnosis of and treatment for disease of the biliary tract at the annual meeting of the American Gastro-Enterological Association in May, 1927, Dr Louis Gregory Cole pointed out that there was a great difference of opinion as to the merits or demerits of drainage of the biliary tract by means of the duodenal tube and that it was still a matter of dispute as to whether it was possible to evacuate the liquid contents of the gallbladder by any manner of intraduodenal stimulation. He thus subjected to recriticism the source of the so-called "B" bile. He suggested the desirability of studying a series of patients by oral cholecystography and drainage of bile by the duodenal tube to see whether the shadow of the dye-filled gallbladder could be made to disappear or be reduced in size, this experiment was to be further controlled by a meal rich in fat, and Dr Cole offered his services for such a study with the purpose of settling this aspect of a controversial topic.

I pointed out to Dr Cole that studies of this kind had already been made in both this country and abroad, some of which had been published. Nevertheless, arrangements were completed to investigate with Dr Cole a series of patients in Philadelphia on May 9, 10 and 11, 1927. Through the courtesy of Prof Willis F Manges, the facilities of his x-ray laboratory at the Jefferson Hospital were placed at Dr Cole's disposal.

Further to control the chief point of the investigation as to whether the gallbladder could be made to empty its dye rich bile by the duodenal tube and further to settle the question as to the source of the "B" bile, it was proposed to estimate quantitatively the iodine content of the "B" and "C" biles, and to Dr G A Williams of the staff of Prof Winthrow Morse was assigned this task.

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## SELECTION OF PATIENTS AND PROCEDURE

For this study nineteen patients were assembled, all of whom were suspected of having, or were known to have, some form of disease of the biliary tract with more or less involvement of the gallbladder. Six were women between the ages of 30 and 60 (average age, 49), and thirteen were men between the ages of 26 and 53 (average age, 40). Seven patients were studied on May 9, six on May 10 and six on May 11.

For the first day's study, the seven patients were given a dinner rich in fat at 6:30 on the previous night, and at 9:30 they commenced to take at fifteen minute intervals two keratinized capsules containing 0.4 Gm of sodium tetraiodophenolphthalein and one capsule containing 0.3 Gm of sodium bicarbonate until eight and four capsules, respectively, had been taken. The eight capsules of the dye represented a total dosage of 3.5 Gm for an average person weighing from 145 to 160 pounds (65.8 to 72.6 Kg). At Dr. Cole's request, these capsules and directions for taking them were furnished by Dr. William H. Stewart of New York.

For the patients studied on May 10 and 11, Dr. Manges furnished eight capsules each containing 0.4 Gm of a brand of tetiothalein sodium-NNR or a total dosage of 3.5 Gm. Two of these capsules were taken at fifteen minute intervals commencing at 9:30 p. m., three hours after a meal rich in fats. All patients reported at the Jefferson Hospital Clinic at 8 o'clock the following morning without having had further food or drink since the previous night at 6:30.

Freshly sterilized duodenal tubes with individual syringes and glassware were used, and the drainages were conducted by Misses Gledhill and LeVan, under the supervision of Drs. Lyon and Swalm. The duodenal tube was passed, the fasting residuum was removed, the stomach lavaged and the tube allowed to pass into the duodenum in the usual manner, and stimulations were given with from 30 to 75 cc of magnesium sulphate solution (33 per cent volumetric), from 50 to 100 cc of a 10 per cent solution of peptone and 30 cc of olive oil. In most cases only one of these stimulants was used, in other cases, all three were given. When the tube was considered to have reached the duodenum, the patient was sent to the x-ray department, and under the supervision of Dr. Cole and Mr. Kelly a first film was made, representing as nearly as possible, a twelve hour exposure of the region of the gallbladder following the use of the dye<sup>1</sup>. The patients were then returned to the drainage room and biliary drainage continued until the sixteenth hour period, when the second x-ray film was made, following this the duodenal tube was withdrawn and the patient sent out for a luncheon rich in fats, the third film was made, as nearly as possible, one hour later. The luncheon consisted of two poached eggs, two slices of bacon, two slices of bread and butter and one glass of half milk and half cream.

On the second and third day's study, the procedure was changed to this extent: drainage was continued until an additional picture was made at the eighteenth hour period before the meal rich in fats and a fourth picture one hour later. While still wet the films were given a preliminary reading by Drs. Cole and Lyon, and the following day and subsequently were given final readings individually.

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1 In several patients, from whom bile was freely drained before the first film was made, it was found that after they walked a distance of nearly 100 yards to the x-ray room the tube had been withdrawn from 2 to 5 inches (5 to 12.7 cm), and the x-ray showed the tip at the pylorus or within the stomach. To prevent this, the patients were subsequently taken to the x-ray room in a wheel chair.

by Drs Cole and Manges. The degree of density of the shadow of the dye was graded upward from 1 to 4. In this report the readings of Dr Cole have been used.

All "B" and "C" biles drained were sent under code numbers to the chemical department for estimation of iodine content. The following method was used for determining the amount of iodine. Three cubic centimeters of bile was placed in a nickel crucible with 1 cc of concentrated sodium hydroxide solution and 0.5 Gm of potassium nitrate, and the mixture evaporated to dryness on the electric hot plate. The crucible was then heated over a small flame until the residue melted, and then the molten mass heated to redness for thirty seconds. After cooling, the fused mass was dissolved in 20 cc of distilled water. The solution was made distinctly acid to litmus by the addition of tenth-normal hydrochloric acid. In most cases, 3 cc of acid sufficed. Five cubic centimeters of chloroform was then added, and the whole shaken vigorously in order to extract the iodine. The supernatant liquid was decanted from the chloroform and the colored chloroform solution of iodine titrated against five hundredth-normal sodium thiosulphate in the usual manner with starch as the indicator. The iodine content was reported in terms of milligrams of iodine per cubic centimeter of bile.

This study was designed to prove two points: (1) that the gallbladder can empty its liquid contents following intraduodenal stimulation, and (2) that the gallbladder represents the source of the "B" bile.

Before the results are reported, it is desirable that a short review of certain previous work be placed in evidence. Some of this is furnished by surgical observation of the gallbladder, some by experimental work on various animals, and some by clinical investigations similar to the present study.

The general principles which we originally and subsequently advanced<sup>2</sup> in regard to biliary drainage have been confirmed by a large

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2 Lyon, B. B. Vincent. *Diagnosis and Treatment of Diseases of the Gallbladder and Biliary Ducts*, J. A. M. A. **73** 980 (Sept.) 1919, *Some Aspects of the Diagnosis and Treatment of Cholecystitis and Cholelithiasis*, M. Clin. N. Amer. **3** 1253 (March) 1920, *The Treatment of Catarrhal Jaundice by a Rational, Direct and Effective Method*, Am. J. M. Sc. **159** 503 (April) 1920, *Need of Early Diagnosis and Treatment of Biliary Tract*, New York M. J. **112** 23 (July 3) 1920, **112** 56 (July 10) 1920, *Can the Gallbladder, Biliary Ducts and Liver be Medically Drained?* Am. J. M. Sc. **160** 575 (Oct.) 1920. Lyon, B. B. V., Bartle, M. I., Ellison, R. T., and Richardson, R. *Discussion of the Treatment of a Case of Chronic Arthritis, with Lambliasis, by Duodenal Biliary Drainage*, M. Clin. N. Amer. **4** 1153 (Jan.) 1921. Lyon, B. B. V., Bartle, H. J., and Ellison, R. T. *Some Lessons Learned from Duodenobiliary Drainage*, Am. J. M. Sc. **162** 60 (Jan.) 1922, **162** 223 (Feb.) 1922. Lyon, B. B. V. *A Reply to Certain Antagonistic Criticism of Nonsurgical Biliary Tract Drainage*, New York M. J. **115** 269 (March) 1922, **115** 456 (April) 1922. *A Brief Consideration of Nonsurgical Gall Tract Drainage as an Aid to the Surgeon*, Penn. State M. J. **25** 392 (March) 1922, *Nonsurgical Drainage of the Biliary Tract*, Philadelphia, Lea & Febiger, 1923, *The Value of Nonsurgical Drainage of the Biliary Tract as a Therapeutic Measure*, Med. C. N. Amer. **8** 803 (Nov.) 1924, *What Shall We Do with and for Our Cases of Gall Tract Disease?* Therap. Gaz. **40** 766 and 854 (Nov. and Dec.) 1924, Lyon, B. B. V., and Swalm, W. A. *Giardiasis: Its Frequency, Recognition, Treatment and Certain Clinical Factors*, Am. J. M. Sc. **170** 348 (Sept.) 1925. *The Therapeutic Value of Nonsurgical Drainage of the Biliary Tract*, J. A. M. A.

majority of observers throughout the world who have carefully studied the method and have used it intelligently. Their corroborative clinical evidence of its usefulness is overwhelming and is well known to the students of this subject. The critics of the method for the most part, have followed a modified technic of their own usually cutting short the procedure in one way or another. They have thus deprived themselves of much of the diagnostic evidence that is really available and have consequently made various erroneous interpretations. Most of these errors have been pointed out in a previous publication.<sup>2</sup> On the other hand some of the overly fulsome praise published by well meaning proponents has really been harmful to this useful procedure. Furthermore we have learned that duodenobiliary drainage has been exploited by physicians poorly trained in the practice of general medicine and in special technic who improperly select for such treatment patients who manifestly require operation by the type of trained nurse who advertises her proficiency in other technical procedures such as colonic irrigations and by the out and out charlatan who trades on the psychic effect of removing a small amount of bile or bile stained fluid from gullible but purse-fat people whose interest is aroused by the pseudo-scientific patter of such menaces to human health. It is deplorable that such practices exist. It furnishes entirely proper ammunition for some opponents of this method of treatment a certain number of them over-balanced institutions with surgical axes to grind, but in turn it reflects discredit on them as well as on a method the merits and limitations of which are becoming more generally appreciated.

#### SURGICAL EVIDENCE

The surgical attempts in furnishing this proof have usually been failures. Within our knowledge only three surgeons have gone on record as having seen the gallbladder empty in response to intraduodenal stimulation. The failure to observe contraction vermiform movement or collapse of the gallbladder more frequently has probably been due to the effects of anesthesia operative injury or shock or handling of viscera. A review of the adverse reports however will show that almost without exception the dark colored bile was recovered through the duodenal tube when the operator manually emptied the gallbladder. Some form of

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85-1541 (No. 14) 1925. Lyon, B. B. V. The Evolution of Early to Late Gall Tract Disease. *Memphis M. J.* 3:67 (March) 1926. Quelques considerations sur l'évolution du diagnostic et le traitement—des affections du tractus biliaire. *Presse med.* 34:361 (Oct.) 1926. The Nature, Diagnosis and Treatment of Cholecystitis, *M. J. & Rec.* 126:620 (No. 16) 1927. 690 (Dec. 7) 1927, Duodenal Tube and Its Practical Value. *Lancet* 2:918 (Oct. 29) 1927. Lyon, B. B. V., and Swalm, W. A. Obstruction of the Cystic Duct of a Catarrhal Variety. *J. A. M. A.* 90:833 (March 17) 1928.

3. Lyon et al. (see note 2 eighth reference)

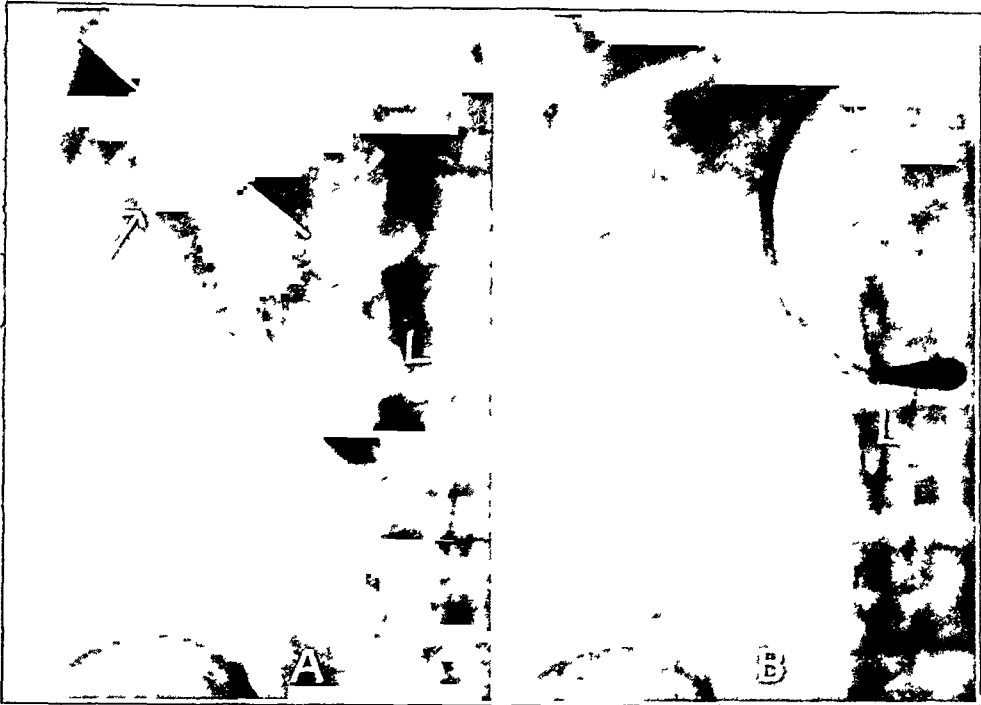


Fig 1 (case 95134) —*A*, twelve hour film, showing shadow of gallbladder before drainage *B*, sixteen hour film, three and a half hours after stimulation with 33.3 per cent magnesium sulphate solution, 140 cc of brownish-black bile, rich in iodine was recovered, associated with disappearance of the shadow.

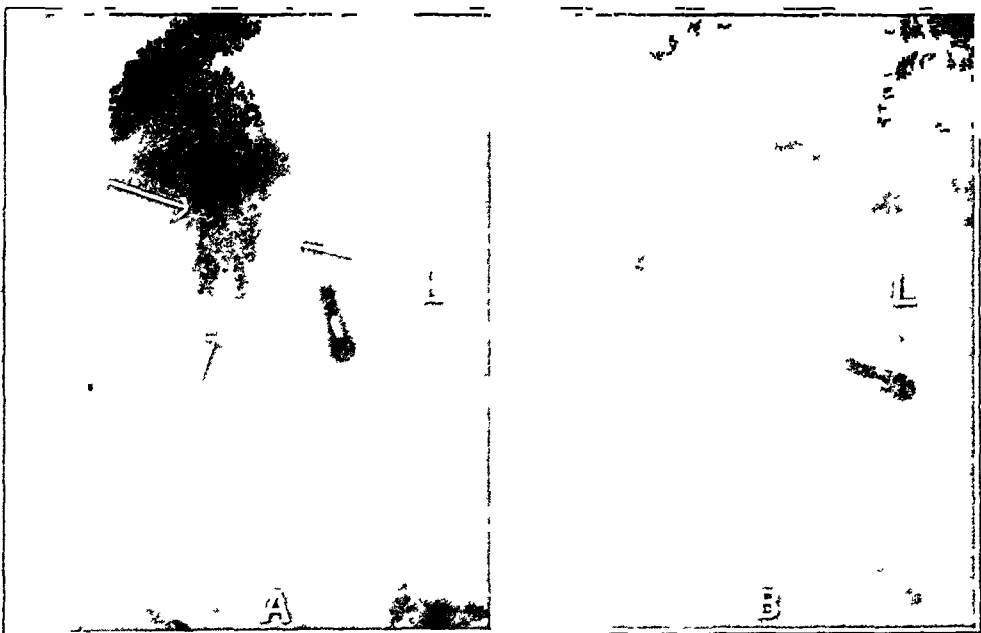


Fig 2 (case 95136) —*A*, twelve hour film, showing shadow of gallbladder before drainage *B*, sixteen hour film, three and a half hours after fractional stimulation with 33.3 per cent magnesium sulphate solution, 192 cc of dark brown bile, rich in iodine, was recovered, with disappearance of the shadow.

obstruction of the cystic duct could account for the exceptions. It might be a matter of interest to have the observations of these three men put on record in this report.

In 1921, Prof. Adolph Sachs<sup>4</sup> of Nebraska reported the following cases, which have been abbreviated somewhat but without alteration of their context.

CASE 1—Mrs. A. H., referred by Dr. G. Simanek, on medical drainage three days prior to operation showed "A" bile a light golden yellow, "B" bile a dark static bile, "C" bile a light lemon yellow. I was permitted to pass the duodenal tube in the above patient before she was anesthetized. The gallbladder was exposed and found to be fairly well distended, and before any exploration was made, 50 cc. of a 33.3 per cent solution of magnesium sulphate was introduced directly into the duodenum through the duodenal tube. In three minutes, bile started to flow. In five minutes, we started to get a real, dark golden bile (typical "B" bile) and the distended gallbladder gradually collapsed. I might compare this to the collapse of a balloon when the air is released (no contraction was observed). The gallbladder was then removed in the usual manner, and the bile in the collection bottle was apparently the same as that obtained from the removed gallbladder, only in greater dilution. I grant this was done under anesthesia and hence open to some objection, however, I offer it for what it is worth.

CASE 2—Mrs. F. was referred by Dr. Simanek for medical drainage and treatment. On three successive medical drainages, only two types of bile were obtained, "A" and "C" bile. The case was referred back for operation as one not suitable for medical drainage. A diagnosis of stones, with probable obstruction of the cystic duct, was made. The duodenal tube was introduced before operation, as in the foregoing case. The usual gallbladder incision was made, the gallbladder exposed, and a small contracted gallbladder was seen. Fifty cubic centimeters of a 33.5 per cent solution of magnesium sulphate solution was introduced into the duodenum through the duodenal tube. No static bile appeared in five minutes, and the gallbladder remained unchanged. The gallbladder was then palpated and found to contain stones. It was removed and on opening it a stone was found, occluding the cystic duct.

CASE 3—From the history and examination of Mrs. H., aged 35, a diagnosis of cholelithiasis was made. On several drainages, we found that at times "B" bile was present and at times not. The duodenal tube was passed as in the foregoing cases and a moderate sized gallbladder was exposed. We stimulated with magnesium sulphate, and no change took place. On light palpation, a stone in the cystic duct was found. This was easily pushed back, and "B" bile appeared, which was apparently the same as that found in the removed gallbladder. There were several calculi present.

In 1923, Pribram<sup>5</sup> of Austria reported as follows:

Einhorn's duodenal tube was inserted before the operation, then a typical yellow-colored bile flowed out, and the abdomen was opened under ether narcosis. After the olive was ascertained to be in its proper position, 20 cc. of a 10 per cent Witte

<sup>4</sup> Sachs, A. Lyon-Meltzer Gall Bladder Drainage, Nebraska M. J. 6:225 (Aug.) 1921.

<sup>5</sup> Pribram, E. E. Peptone Gallbladder Reflex, Klin. Wchnschr. 2:1590, 1923.

peptone solution was introduced through the duodenal tube, and a dark, thick, oily bladder bile was recovered through the tube. The gallbladder contracted distinctly, and after several minutes a yellow liver bile again ran out.

In 1924, Matsuo<sup>6</sup> of Japan reported the two following cases.

CASE 1—F S, aged 37, according to the diagnosis made previous to operation, had a tumor in the left liver lobe. At operation, Oct 27, 1923, a gallstone was found in the liver. As the disappointments resulting from operations performed by Lyon and others are explained by the fact that narcosis was induced, I wished to avoid this factor, not only was the patient not put under general narcosis, but also the pantopon-scopolamine solution was not injected. The abdomen of the patient was opened according to Kocher's technic under local anesthesia produced by procaine-epinephrine. By means of the usual incision, the gallbladder, which was as large as a good sized egg, was exposed, it was so greatly distended that the small blood vessels were scarcely visible.

Two hours before the operation, the duodenal tube was given to the patient, its proper location being determined by the roentgen rays.

The gallbladder was 7.5 cm in length, measured from the point at which the gallbladder was attached to the inferior surface of the liver, and 4.5 cm in breadth. During the operation, the duodenal content mixed with the typical bright yellow bile was flowing out. Then 40 cc of a 33 per cent magnesium sulphate solution was introduced into the duodenum through the tube. Five minutes afterward, the typical brown bile, the so-called "B" bile, began to appear, the amount was 80 cc. Finally, after thirty-five minutes, the bright yellow bile ran out again.

At first the gallbladder was entirely filled, and it seemed so expanded that the blood vessels could not easily be seen. However, as the magnesium sulphate was given, and the dark, thick bile gradually dribbled out, the blood vessels became quite visible, standing out thickly, the gallbladder was no longer expanded, and, gradually decreasing in size, it was reduced at last to 4 cm in length and 2.6 cm in breadth. The so-called contraction was not observed, nor did the bladder collapse like a balloon from which the air was released, according to the description of Simanek. Rather, the size of the gallbladder decreased in an instant, estimated merely by the eye, the organ became one-fourth its previous size.

Forty cubic centimeters of a 1 per cent azorubin S solution was then injected into the gallbladder, which almost resumed its original size. This procedure was painful to the patient. The organ, however, did not become nearly so large as before, being 5.5 cm in length and 4.5 cm in breadth. During this procedure, the bile from the duodenal tube had no trace of any red color. Forty cubic centimeters of a 33 per cent magnesium sulphate solution was then sent through the tube again, and this time it was observed that the gallbladder contracted very clearly and that almost all the dye solution was evacuated in a short time.

Judging from these results, I believe that, beyond any question, the bile flows out from the gallbladder into the duodenum by reason of the local application of magnesium sulphate.

CASE 2—Z O, aged 25, was operated on Feb 14, 1924, for chronic appendicitis. Under the same conditions as those stated in case 1, observations were made with the assistance of Dr Tsuji. Before the operation the olive was ascertained by

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<sup>6</sup> Matsuo, Iwao. Magnesium Sulphate as a Cause of the Evacuation of the Gall Bladder, J A M A 83 1289 (Oct) 1924.

means of the roentgen ray to be in its proper position, but from the time that the gallbladder was exposed, the bile ceased to flow out, and the instillation of magnesium sulphate solution did not bring about the appearance of the bile. Then it was found by palpation that the olive was far from the proper position required, that is, in the ascending part of the pars horizontalis inferior duodeni. When the olive was withdrawn to the proper position, near the papilla of Vater, the gallbladder was filled with 35 cc of a 1 per cent azorubin S solution, and the bile that ran out was not stained red. The instillation of 40 cc of a 33 per cent magnesium sulphate solution was made, and two minutes afterward bile, colored deep red by dye, began to flow out, in the first five minutes, 45 cc was recovered, and in the next five minutes 42 cc. The patient vomited a deep red bile. At this time, the gallbladder became small, although nothing like contraction could be observed to be taking place.

It is evident that the manner in which the gallbladder is observed to empty varies somewhat, although both Pribram and Matsuo definitely described it as a contraction. Yet, in these six cases, it appears that the gallbladder, unless too diseased or associated with obstruction of the cystic duct, will empty its liquid contents wholly or in part as a dark colored bile comparable to the "B" fraction.

#### EXPERIMENTAL EVIDENCE

I shall now consider contributions from the experimental laboratory. Investigations into the function of the gallbladder and especially in regard to its method of emptying have long engaged the interest of physiologists. Between 1893 and 1923 the hypotheses, based on experiments conducted, were greatly at variance, divergent results being obtained by various investigators, so that much confusion of ideas has existed. Since the various theories have been recently restudied carefully by Whitaker and by Higgins and Mann, they will not be reviewed here in detail. I shall place in evidence only the most authoritative opinions of the present day.

In 1923 and subsequently, Boyden<sup>7</sup> was first able to demonstrate that a meal rich in fats (egg yolk and cream) "induces the following cycle of changes in the gallbladder of the cat: (1) a period of slow emptying (two hours), (2) a collapsed or resting period marked by rearrangement of the mucosa (five hours) and (3) a period of rapid filling and bile concentration." Protein, such as egg white, and carbohydrate failed to provoke a similar response.

In 1926 Higgins and Mann<sup>8</sup> confirmed Boyden's results on certain fishes, amphibia, birds and mammals, finding that the gallbladder

7 Boyden E. A. Effect of Natural Foods on the Distention of the Gall Bladder with a Note on the Changing Pattern of the Mucosa Under Distention and Collapse, *abstr.*, *Anat. Rec.* **24** 388, 1923, **30** 333, 1925, *Anat. Rec.* **33** 201, 1926.

8 Higgins G. M., and Mann, F. C. Observations on Emptying of the Gall Bladder, *Am. J. Physiol.* **78** 339 (Oct.) 1926.

emptied in response to a meal rich in fats in from one and one-half to three hours irrespective of whether the animal was carnivorous or herbivorous in its normal habits. They then investigated the mechanism by which such emptying occurred in careful experiments on the garpike, guinea-pigs and dogs, and they concluded that (1) the gallbladder empties through the cystic duct, (2) the gallbladder empties by contraction of its own intrinsic musculature, (3) secretory pressure is of little significance in emptying the vesicle, (4) intra-abdominal pressure is not a major factor in emptying the vesicle, and (5) the sphincter of the common duct is not a factor in emptying the vesicle, except that its relaxation permits the bile to pass to the duodenum under pressure incited by the contraction of the gallbladder.

In their studies on the exposed gallbladder after the meal rich in fats, these authors also found that there are localized areas of contraction, described as follows:

The spherical bladder very gradually becomes somewhat hexagonal or pentagonal in outline, as its major axes reduce in dimension. Very frequently we have noted such extensive localized contractions as to induce the formation of numerous knob-like diverticula over the entire fundus of the vesicle x x x x. Under the experimental conditions the vesicle never entirely emptied its bile, as it had been observed to do in the killed animal.

In 1926, Whitaker,<sup>9</sup> after filling the gallbladder of dogs and cats with iodized oil and following its movement with the x-ray, came to the following conclusions: 1 The gallbladder is shown to empty its contents into the duodenum during the digestion of fats. 2 This emptying is produced principally by the muscular tunic of the gallbladder, extrinsic mechanical factors not having an appreciable effect. 3 Emptying probably does not depend on a reflex nervous mechanism involving extrinsic nerves since vagal stimulation has no effect, and denervated gallbladders empty normally. 4 There is no direct evidence that the expulsive action of the gallbladder is due to a hormone, although it invariably depends on the digestion and absorption of proteins or fats, especially the latter. 5 The action of the so-called sphincter papillae seems to be to allow the gallbladder to fill during the intervals between periods of digestion, but the vesicle will not empty after the sphincter is cut, feeding being necessary, as in normal animals, to effect this result.

It is of interest that Boyden and Whitaker found "that simply putting the cat under ether anesthesia, opening the abdominal cavity and

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<sup>9</sup> Whitaker, L. R. Mechanism of the Gall Bladder, *Am J Physiol* **78** 411 (Oct.) 1926, Experiences with Cholecystography, *J A M A* **86** 239 (Jan 23) 1926, Mechanism of the Gallbladder and Its Relation to Cholelithiasis, *ibid.* **88** 1542 (May 14) 1927, Diagnosis of Gallbladder Disease, *ibid.* **88** 1791 (June 4) 1927.



quickly closing it will delay the gallbladder emptying for several hours. Deep ether anesthesia alone will prevent it. Even slight illness, such as wound infection may greatly inhibit emptying."

To the experienced observer of biliary drainage, deviation from the normal drainage response will often occur in sick patients who have diseased gallbladders, and not infrequently in sick or nervous patients with apparently normal gallbladders.

Hamrick's<sup>10</sup> conclusions from his experimental studies on the emptying of the gallbladder, which were reported in 1927, are closely in agreement with those of Whitaker and of Higgins and Mann.

The uniformity of agreement of these later investigators, when using similar methods of more modern development, should have considerable weight in explaining the divergent opinions of Doyon, Freese, Westphal, Bainbridge, Sweet, Halpert, Winkelstein, Diamond, Graham and other experimental workers with animals.

#### CHOLECYSTOGRAPHIC EVIDENCE

I shall now examine the evidence from various cholecystographic studies combined with duodenal intubation and biliary drainage.

In 1924, Silverman and Menville<sup>11</sup> were the first to demonstrate on human beings that the shadow of the dye-filled gallbladder could be substantially reduced in size and altered in shape following intraduodenal stimulation with magnesium sulphate. (The films of this study were exhibited at the meeting of the American Medical Association in 1924 and published in 1925.) The methods then used were less well established and the results less convincing than the films subsequently sent from various observers, notably Mariano Castex of Buenos Aires, Comstock of Saratoga, Lake of New York, Eberhard of Philadelphia and others. These films show clearly the marked reduction in size and shape of the dye-filled gallbladder that occurs after intraduodenal use of magnesium sulphate, which is promptly followed by the recovery of dark brown to black bile, usually within from ten to thirty minutes.

In 1926, Whitaker<sup>12</sup> confirmed the work of Silverman and Menville, although he, too, was unable to secure evidence of complete emptying of the gallbladder by such a procedure and stated that "we have found that almost invariably the decrease in size of the gallbladder shadow is greater if the patient has taken food especially fat, than after the

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10 Hamrick, R. C. Emptying of the Gall Bladder, *Am J M Sc* **174** 168 (Aug) 1927.

11 Silverman, D. N., and Menville, L. J. Observations of the Visualized Gall Bladder by Graham Method, with Reference to the Effect of Nonsurgical Biliary Drainage, *J A M A* **84** 416 (Feb 7) 1925.

12 Whitaker (footnote 9, second reference)

intraduodenal injection of magnesium sulphate. This raises the question as to the value of nonsurgical biliary drainage by such means."

The improved results obtained in the present study equally raise the question as to the technic of intraduodenal drainage of the gallbladder which is employed.

The most recent utilization of this method of determining the source of the "B" bile has been undertaken by Lake,<sup>13</sup> who reported in December, 1927, the results of a study of eighteen patients. By means of magnesium sulphate either alone or followed by olive oil given intraduodenally, he recovered a good "B" bile fraction and caused marked reduction in the size of the shadow in five of eight cases, slight reduction in two and total disappearance of the shadow in one. In the latter instance, magnesium sulphate alone was used. To make a further check on the source of "B" bile, Lake had the various fractions of bile quantitatively tested for iodine (following the use of tetraiodophenolphthalein), and in this group found the "B" fractions to contain 10.8 times as much iodine as the "C" fractions and forty-eight times as much as the "A" fractions. In four of five cases in which small or doubtful "B" fractions were recovered only a slight reduction of shadow was obtained, and in one no reduction. In this group the "B" bile contained less iodine and the "C" more than in group 1. In five patients who failed to deliver "B" bile, two did not show a gallbladder shadow, one showed a mottled shadow, one a semilunar shaped shadow and one an apparently normal shadow. "In no case did the shadow decrease in size following the drainage. The iodine content of these biles was about the same before and after the stimulation, only traces being found or none at all."

Lake summarized his study as follows:

1 The recovery through a duodenal tube of 1 ounce or more of brownish, dark greenish or black bile following the instillation of magnesium sulphate or olive oil is accompanied by a considerable decrease in the size of the gallbladder shadow by the roentgen ray, or (in one case) its disappearance.

2 The dark bile so obtained contains an average of 43 times as much iodine as the bile that precedes it and 10.8 times as much as the bile that follows it, and may be the only fraction containing any iodine (fourteen hours after the oral administration of sodium tetraiodophenolphthalein).

3 When no dark bile is recovered, even though large amounts of yellow bile appears, the gallbladder shadow is either absent or does not decrease in size.

4 When a smaller amount of dark bile or a larger amount of amber-colored bile is secured, the gallbladder shadow decreased slightly in size or (in one case) not at all.

**Conclusion.** The above results seem to indicate that samples of bile from the gallbladder can be recovered through the duodenal tube for microscopic and bacteriologic examination.

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13 Lake, M. Observations on the Origin of the "B" Bile Obtained by Lyon's Method of Biliary Drainage, *Am J M Sc* **174** 786 (Dec) 1927.

It will be seen, therefore, that there already exists a large amount of evidence indicating that, with rare exceptions which can usually be accounted for, the gallbladder is the source of the dark colored bile ("B" fraction) recovered after intraduodenal stimulation with magnesium sulphate, peptone or olive oil. Oleic acid, as recommended by McClure and others, is also a good intraduodenal stimulant for evacuation of the gallbladder.

Ivy and Oldburg<sup>14</sup> recently announced that the duodenal mucosa contains a secretin which can be isolated and when injected intravenously will provoke evacuation of the gallbladder. In this connection it might be worth while to state that a French preparation of secretin prepared by Les Etablissements BYLA for Professor Chiray of Paris for stimulating the flow of external pancreatic secretion was obtained by us on a recent visit to Paris. Following the publication of Ivy and Oldburg, we tried out this French preparation using 3 cg intravenously before any other stimulants were given on patients undergoing biliary drainage. Thus far, in eighteen tests on sixteen patients there has been recovered only a trace of "B" bile in four and none whatever in fourteen within from forty-five to sixty minutes after the injection of secretin, although good specimens of "B" bile were subsequently recovered within from two to thirty minutes after stimulation with magnesium sulphate in fifteen of the eighteen tests. It may be that Ivy's secretin contains a specific gallbladder "principle" which is absent in the French preparation.<sup>15</sup>

Various men have sought to show that the source of the "B" bile is not necessarily the gallbladder. The case reported by Dunn and Connell<sup>16</sup> in 1921, suggesting a possible extra vesicle source for "B" bile, was for a time the most difficult one to interpret correctly.

In 1922, we<sup>3</sup> pointed out that it might be possible to recover a dark colored bile from a cholecystectomized patient with a dilated extra hepatic or intrahepatic duct system, or in hepatic cirrhosis associated with long continued biliary obstruction, and we suggested that this might be the explanation of the recovery of such static bile as was reported by Dunn and Connell in their patient who had had fifteen operations on the biliary tract.

It was not until 1926 that rather conclusive proof of this assumption was furnished by Counseller and McIndoe,<sup>17</sup> who showed the dilatation

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14 Ivy, A. C., and Oldberg, E. Contraction and Evacuation of the Gall Bladder by a Purified "Secretin" Preparation, *J A M A* 90 445 (Feb 11) 1928

15 This study will be reported more fully elsewhere

16 Dunn, A. N., and Connell, K. Report of a Case of Hepatoduodenostomy with Some Observations on the Lyon-Meltzer Method of Biliary Drainage, *J A M A* 77 1093 (Oct 1) 1921

17 Counseller, V. S., and McIndoe, A. N. Dilatation of the Bile Ducts (Hydrohepatosis), *Surg Gynec Obst* 43 729 (Dec) 1926

of the biliary tree which takes place in chronic partial or complete obstruction of the extrahepatic duct system or in chronic calculous cholecystitis. We believe that those experienced in biliary drainage will agree that patients so studied after cholecystectomy will usually fail to deliver a "B" fraction, and that in the occasional exceptions a review of the case will indicate the likelihood of dilated ducts with sacculi or intrahepatic stasis. Such patients usually are jaundiced, have chronic disease of the liver or have had several operations on the upper part of the abdomen. With this review of previous evidence bearing on the subject, I shall report the results of the present study.

#### REPORT OF PRESENT STUDY

Four of nineteen cases were discarded from analysis because of failure to intubate the duodenum for reasons which will be discussed later. The remainder (fifteen cases) have been divided into two groups, the first of which requires little if any discussion. In six patients (numbers 95096, 95105, 95134, 95136, 95137 and 95171) of group 1 (table 1) in whom after oral administration of the dye excellent gallbladder shadows appeared and in whom good "B" fractions rich in iodine were recovered, the shadow was made completely to disappear after biliary drainage, as shown in the accompanying illustrations. Four of these patients had three fractional magnesium sulphate stimulations, one had one magnesium sulphate stimulation, which recovered 70 per cent of the "B" fraction, followed by olive oil, which recovered the remaining 30 per cent, and one had one peptone stimulation alone.

The duration of drainage averaged three hours and ten minutes, although in most cases all of the "B" bile was recovered within the first ninety minutes. It is worthy of comment that in all of these six patients the position of the duodenal tube as shown by the x-rays was favorable for good drainage, all of them had had a good night's sleep and none were nervous. Clinically, none showed advanced pathologic changes in the gallbladder, although all had symptoms, some physical manifestations and bile suggestive of those of early cholecystitis. The amount of "B" bile recovered ranged between 100 and 192 cc, averaging 142 cc, the amount of "C" bile recovered ranged between 190 and 750 cc, averaging 428 cc. The amount of iodine in "B" biles ranged between 34 and 96 mg per cubic centimeter of bile. The amount of iodine in "C" biles ranged between 0.42 and 3.2 mg per cubic centimeter of bile. The "B" bile iodine, averaging 6.9 mg, was more than four times as strong as the "C" bile iodine, which averaged 1.6 mg. In this group are also included two patients, one of whom (95133) had had a poor night with diarrhea (four stools) and slight nausea. The tube was in poor position twelve hours after intubation but had reached a good position before the sixteen hour picture was

TABLE 1 —Data in Group 1

Case Number	Sex	Age	Reaction to Capsules	Position of Tube at			Density of Gallbladder Shadows			Reduction in Size of Shadow	Iodine, Mg per Ce		Ce of Bile		Stimulation Used
				12 Hours	16 Hours	20 Hours	12 Hrs	16 Hrs	18 Hrs		"B"	"C"	"B"	"C"	
9496	F	30	0	Good	Good	Good	1	0	0	Complete	12	25	120	210	MgSO <sub>4</sub>
9505	M	51	0	Good	Good	Good	2	0	0	Complete	9.6	0.12	100	.00	MgSO <sub>4</sub> and oil
95134	M	40	0	Good	Good	Good	1	1	0	Complete	6.1	3.2	110	500	MgSO <sub>4</sub>
95136	M	15	0	Good	Good	Good	1	0	0	Complete	8.1	0.8	192	176	MgSO <sub>4</sub>
95137	M	53	0	Good	Good	Good	1	0	0	Complete	3.1	1.3	125	100	Peptone
95171	M	23	0	Good	Good	Good	3	0	0	Complete	9.5	1.1	175	750	MgSO <sub>4</sub>
95173	M	17	Nausea, diarrhea	Poor	Good	Good	2	0	0	Complete	1.2	1.5	125	470	MgSO <sub>4</sub> and oil
95138	M	37	Diarrhea	Poor	Poor	Poor	1	1	2	1/4	1.2	n t	125	100	Oil

TABLE 2 —Data in Group 2

Case Number	Sex	Age	Reaction to Capsules	Position of Tube at			Density of Gallbladder Shadows			Reduction in Size of Shadow		Iodine, Mg per Ce		Ce of Bile		Stimulation Used
				12 Hours	16 Hours	20 Hours	12 Hrs	16 Hrs	18 Hrs	B D *	M†	"B"	"C"	"B"	"C"	
95095	M	35	0	Good	Good	Good	0	0	0	Complete	Complete	6.2	0.42	95	150	MgSO <sub>4</sub>
95100	M	16	Nausea, pylorospasm	Poor	Good	Good	3	0	0	0	0	10.5	0.4	145	375	MgSO <sub>4</sub>
95135	M	19	Nausea, pylorospasm	Poor	Good	Good	1	1	1	1/4	1/2	6.4	1.1	170	200	M-P-O‡
95102	M	52	Nausea, pylorospasm	Poor	Good	Good	1	2	?	0	?	3.5	0.6	100	350	M-P-O
95175	F	55	0	Good	Good	Good	1	2	1	1/4	0	3.6	1.3	205	250	MgSO <sub>4</sub>
95172	M	26	0	Good	Good	Good	3	1	3	1/2	1/2	19.6	3.2	100	400	M-P-O
95170	M	11	Nausea, vomiting, diarrhea	Good	Good	Good	1	2	1	1/2	0	17.9	0.8	90	230	M-O§

\* B D indicates reduction in size of shadow after biliary drainage

† M indicates reduction in size of shadow after meal rich in fats

‡ M-P-O indicates MgSO<sub>4</sub> peptone oil§ M-O indicates MgSO<sub>4</sub> oil

taken The iodine concentration of 4.2 mg in "B" bile as compared to 1.5 in "C" bile suggested poor filling of the gallbladder. The dye shadow of grade 2 density disappeared after the diamage between the twelfth and eighteenth hour picture. Cholecystectomy and appendectomy were performed on this patient in December, 1927, and the following pathologic conditions were noted: chronic atrophic non-calculous cholecystitis and pericholecystitis, fibrous tissue in the liver, which was more distinct than usual, chronic adhesive appendicitis, a healed scar left by an ulcer on the duodenum, and mild colitis of the transverse colon.

In the second case (95138) a grade 4 shadow density was reduced to grade 1 after diamage in spite of the unsatisfactory position of the tube in a patient who was nervous after a poor night due to diarrhea. Here, too, the iodine content of 4.2 mg in "B" bile was surprisingly low for a gallbladder that had apparently filled and concentrated well.<sup>18</sup> However, it must be noted that even after a meal rich in fats the gallbladder had not completely emptied.

In group 2 (table 2) are included seven patients, five of whom clinically showed a more advanced pathologic condition of the gallbladder and two of whom had had obstructive jaundice two months previous to this study. One of these (95100) failed to show a shadow of the gallbladder on the films made at the twelfth, sixteenth or eighteenth hour and likewise failed to deliver any "B" bile, although 550 cc of "C" bile was obtained with an average iodine content of 2.2 mg. In addition this patient had nausea and pylorospasm with gross retention of food after twelve hours of fasting, and the duodenal tube was in a poor position. From the other recently jaundiced patient 170 cc of "B" bile drained (after combined stimulation) which contained 6.4 mg of iodine, the shadow of the gallbladder became distinctly smaller, although the degree of density did not change even after a meal rich in fats. The iodine of the "C" fraction, which amounted to only 200 cc of bile, was 1.4 mg. Since Dr. Manges noted that the shadow of the liver was more dense, possibly poor elimination of the dye may account for poor density of the gallbladder. One hundred cubic centimeters of "B" bile of low iodine content (3.5 mg) drained from a third patient (95102) after stimulation with magnesium sulphate, but failed materially to reduce the size of the gallbladder or its density of grade 1 until after the ingestion of a meal rich in fats, possibly the "B" bile with low iodine content represents thick "B" bile with poor iodine admixture. A fourth patient (95175) gave practically the same result. The next two patients are of interest. The first (95172) showed a good gallbladder shadow, which was reduced somewhat in size

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18 In this patient the "C" bile was not tested.

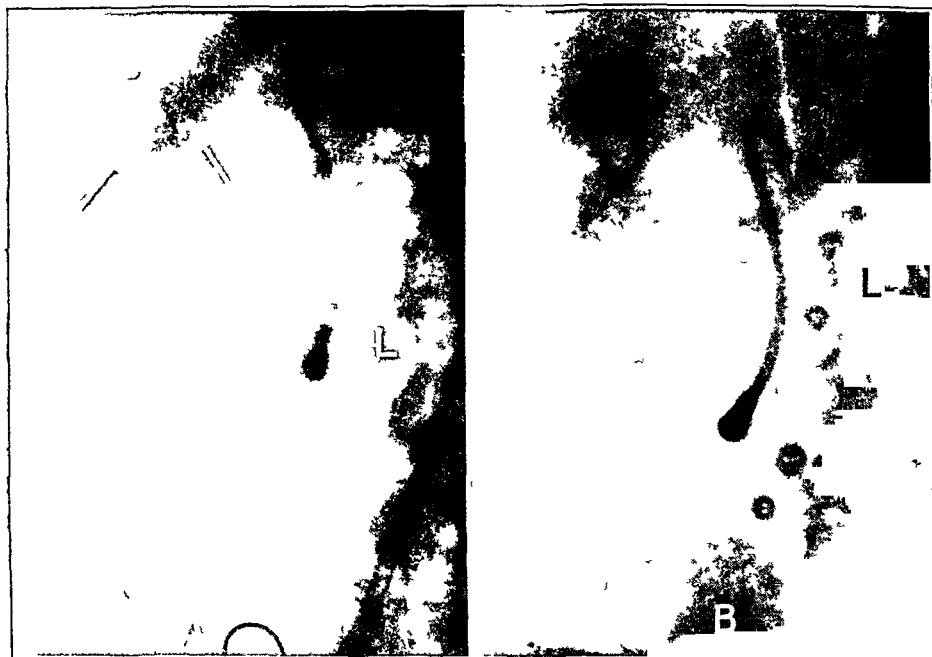


Fig 3 (case 95137)—*A*, twelve hour film, showing shadow of gallbladder before drainage *B*, sixteen hour film, three and a half hours after stimulation with 50 cc of 10 per cent peptone, 125 cc of blackish-brown bile was recovered The shadow disappeared

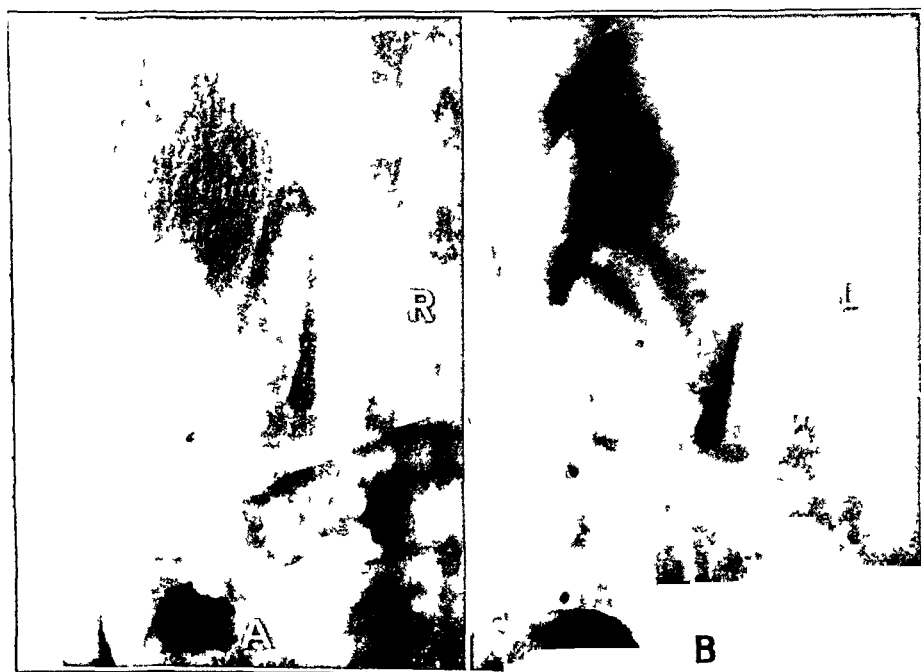


Fig 4 (case 95171)—*A*, twelve hour film, showing shadow of gallbladder before drainage *B*, eighteen hour film, about five and a half hours after fractional stimulation with 33.3 per cent magnesium sulphate solution, 175 cc of greenish-black bile, rich in iodine, was recovered The shadow disappeared

but which failed to empty after either drainage or a meal high in fat content, although 100 cc of normal "B" bile was obtained which contained the surprisingly high iodine content of 196 mg. The second patient (95170), who was nervous after a poor night due to nausea, vomiting and diarrhea, showed an unsatisfactory shadow not exceeding grade 1 density which diminished to one-half its size after eighteen hours and then emptied completely after a meal rich in fats. From this patient, after the administration of olive oil, we recovered 90 cc of "B" bile with a high iodine content of 178 mg. The high iodine content of these two cases was a surprise and a matter of comment, so that the chemical determination was repeated, with exactly the same result. The interpretation of these cases is difficult, and they should be completely rechecked.

The remaining case in group 2 (95095) is also of interest. The gallbladder could not be visualized on films made at the twelfth, sixteenth or eighteenth hours. Nevertheless, after the administration of magnesium sulphate we secured 95 cc of "B" bile with an iodine content of 62 mg as compared to an iodine content of 0.42 mg in 450 cc of "C" bile. As this patient, whose condition was clinically estimated as early cholecystitis, had always given satisfactory "B" bile recoveries on previous drainages, we were at a loss to account for failure of gallbladder visualization, we repeated the study with Dr. Manges on Feb 7, 1928, at which time a gallbladder shadow of grade 3 density at twelve hours disappeared at fifteen hours following which 145 cc of "B" bile was recovered by drainage after stimulation with magnesium sulphate only. The iodine content in milligrams of this patient's bile fractions was as follows: duodenal fraction, 0.6, "B" bile after first stimulation with magnesium sulphate, 127, after second stimulation, 84, after third stimulation, 23, "C" fraction, 375 cc after stimulation with olive oil, iodine content, 0.4. If this case should be accepted on the basis of recheck study, it would then properly belong to group 1.

In group 3 are placed the four patients (95106, 95107, 95173 and 95174) who were excluded from analysis because of the failure of duodenal intubation. The reasons for this failure are obvious. After the administration of the dye capsules all had poor nights with nausea, vomiting, diarrhea, excessive nervousness and pylorospasm. Three of these patients have definite clinical evidence of cholecystitis. In two of these (95107 and 95174), there was evidence of gross food retention in the contents of the stomach after twelve hours of fasting. One of these patients (95174) was continually nauseated throughout the preliminary gastric lavage and vomited the tube after the first film was made at the twelfth hour period, at which time a gallbladder shadow was not observed. The third patient (95107) showed a shadow of grade 1 density which failed to disappear although it was reduced to one-half its size after a meal rich in fats. In the fourth patient (95173) who



had pylorospasm and probably hyperperistaltic effort, when the tube was withdrawn it was found tied in a knot. In this patient the dye shadow of grade 3 density failed to disappear after a meal rich in fats, although it was reduced to one-fourth its original size.

#### COMMENT AND CONCLUSIONS

From the foregoing resume it is evident, first, that the gallbladder empties its liquid contents largely by means of its intrinsic musculature and that such factors as diaphragmatic pressure, respiratory movements, changes in intra-abdominal pressure, changes in tonicity of the duodenal wall and of Oddi's sphincter, which thus contribute to a milking-like action on the common duct, all play a relatively unimportant rôle. Second, good specimens of gallbladder bile may be obtained by duodenal tube after intraduodenal stimulation with magnesium sulphate, peptone and olive oil and to a lesser degree by some other substances.<sup>19</sup> Third, specimens of gallbladder bile are therefore procurable for direct microscopic chemical and bacteriologic study in the majority of patients with various grades of pathologic changes in the gallbladder except when the cystic duct is obstructed by impaction of a stone, stricture or adhesions. Catarrhal obstruction of the cystic duct furnishes one important differential exception.<sup>20</sup>

The following exceptions, not concerned with block of the cystic duct which prevent recovery of gallbladder bile should also be borne in mind: (a) chronic contracted fibrotic gallbladders, usually containing calculi with thickened walls and destroyed musculature, (b) gallbladder atony to which we have referred in various publications and which appears to be identical with the "gallbladder inertia" described by Chiray and his various associates in the French school. These are probably overstretched gallbladders, some of them with paper thin walls, (c) discoordinated nerve control to the gallbladder and Oddi's sphincter in various neurolabile subjects many of whom show other evidences of an unstable nervous system.

The last two groups make up those persons whom Smithies and his associates<sup>21</sup> have described as exhibiting "physiologic block" as con-

19 Kalk, H. and Schondube, W. Motility of Biliary Passages, Pituitrin Test of Gall Bladder in Catarrhal Jaundice, *München. med. Wchnschr.* **73** 353, 1926. Chiray, M., Lebon, J. and Galligani, H. Action of Certain Stimulants of Vegetative and Endocrine Systems on Contraction of Gall Bladder in Man, *Bull. et mem. Soc. méd. d. hôp. de Paris* **50** 103, 1926. Meyers, S. G. Emptying of the Gall Bladder with Especial Reference to the Use of Pituitrin, *Am. J. M. Sc.* **175** 405 (March) 1928.

20 Lyon (footnote 2, nineteenth reference)

21 Smithies, F., Karshner, C. F. and Oleson, R. B. Nonsurgical Drainage of the Biliary Tract, *J. A. M. A.* **77** 2036 (Dec) 1921.

trasted with "mechanical block" The condition in group A will at all times prevent recovery of gallbladder bile and will give strongly positive cystographic evidence of chronic surgical cholecystitis The patients in groups B and C can usually be made to drain gallbladder bile subsequently in group B, by exercise of the atonic musculature by a dietary rich in fats and by duodenal drainage frequently repeated, in group C, by bromides or other sedatives and antispasmodics such as atropine administered hypodermically or belladonna given by mouth until a physiologic effect is produced

Since this study was designed to prove that the gallbladder can empty its liquid contents following intraduodenal stimulation and that such contents represent the source of the "B" bile, it would have been better if we had selected normal subjects with normal gallbladders We believe it safe to assume that if we had done so, the results in our favor would have more nearly approached 100 per cent

Nevertheless, our results clearly indicate that in patients with unobstructed cystic ducts and less advanced cholecystitis the gallbladder is the source of "B" bile and empties it after intraduodenal stimulation, as demonstrated by group 1, that in group 2, in patients with more advanced pathologic changes, the results, although less good, cannot be construed as vitiating the value of duodenal drainage but merely limit the scope of its therapeutic usefulness, as we have pointed out in earlier publications We have learned by previous clinical experience that many patients representative of group 2 will give so much better results on repeated drainages as to justify, in properly selected cases, a continuance of nonsurgical management

Finally, we hope that as a result of the evidence submitted, further controversy in regard to drainage of the gallbladder by the duodenal tube may be unnecessary

We should now turn our attention to investigating the value of duodenal biliary drainage as an adjunct therapeutic agent in various problem diseases, such as hepatic inflammations, infections and cirrhoses, various hepatic splenopathies, pernicious anemia, diabetes, the medical variety of peptic ulcer, some forms of arthritis, asthma, and epileptoid seizures suspected of hepatic intestinal toxic or infectious origin, and various postoperative sequelae, such as residual cholangitis, adynamic ileus and persistent singultus

Some favorable reports of clinical improvement already exist, and by reason of new advances in physiology and biochemistry many avenues of investigation might be profitably followed

# GALLOP RHYTHM IN HYPERTENSION ~

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Gallop rhythm has long attracted the interest of both the clinician and the physiologist. It has always been regarded as a warning of a serious condition of the patient, and even though the belief that it invariably indicates a fatal issue has had to be abandoned, its grave prognostic significance is still unquestioned. The theories to explain the mechanism have been numerous, and consequently the literature on the subject is prolific.

In this paper, we attempt to elucidate the dynamic factors connected with the production of this extra sound by means of graphic methods, giving exact records of the sounds and their relationship to the electrical and mechanical phenomena of the heart cycle.

We are concerned only with the study of patients presenting the classic syndrome of Potain gallop rhythm in cases of hypertension with more or less marked cardiac insufficiency. This type of patient is frequently found in hospitals, and has been the subject of numerous investigations from many points of view. All varieties of methods, graphic and otherwise, have been essayed on these patients, the literature, however, contains but few actual sound curves, of which the remarkable records of Lewis are the outstanding examples. Most of the other writers on the subject are content with records of the apex beat.

## METHOD

The point of chief importance seemed to be the exact location of the extra sound in the heart cycle. To determine this, we used simultaneous records of heart sounds and electrocardiograms and, whenever possible, recorded also the venous pulse, arterial pulse and apex beat. As many as possible of these records were made simultaneously on the same strip of film, but in any case, an electrocardiogram was included with each set of mechanical records to serve as a standard of measurement. Lead III of the electrocardiogram was generally used.

We had at our disposal only one string galvanometer, which was needed for the electrocardiogram. We were therefore unable to utilize Einthoven's electrical method of recording heart sounds, though it is probably the most satisfactory procedure, as regards both precision and appearance of the records. The only other method approaching the necessary high sensitivity is that of Frank, which we adopted in the form of Wiggers' modification,<sup>1</sup> with a few additional minor changes.

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\* Submitted for publication Sept 15, 1928

\* From the Cardiographic Laboratory of Mount Sinai Hospital

1 Wiggers, C J. Am J M Sc 153 666, 1917

The recording tambour (Frank's capsule) consists of a small metal cup (diameter, 8 mm, depth, 6 mm) with a typical Frank's segment, the cord of which was 6 mm long. As an oscillating membrane, we employ an extremely fine film of rubber. This is freshly prepared immediately before use from a rubber solution readily obtained commercially, and known as rubber cement<sup>2</sup>. The solution is rather viscous, and by means of a glass rod a fine film can easily be drawn over the opening of the tambour. The film adheres closely to the edge of the tambour and vibrates freely. A minute glass mirror, cut from a silvered cover-slip, is placed directly on the membrane near the straight segmental edge, any possible contact of the mirror with the edge of the tambour being carefully avoided, to ensure its free movement. The placing of the mirror is an important point in the technique, this position—near but not touching the edge—has given us the most satisfactory results. The extremely small size and negligible weight<sup>3</sup> of our mirrors make it unnecessary to place them overhanging the edge, as was originally recommended by Frank.

The method as a whole is satisfactory and has the advantages of extreme simplicity and trustworthiness, which by far outweigh its defects. The main drawback lies in the fact that the sensitivity of the rubber membrane varies with the viscosity of the solution used and with changes of the temperature and moisture of the air. On some days we found it extremely difficult to produce a satisfactory sound capsule, but usually the vibration frequency of the membrane was sufficiently high for a reliable sound record. As this study was not concerned with an analysis of the sound vibrations as such, but rather with the determination of the time of their occurrence, we did not have any difficulty in obtaining useful curves with the average capsule.

The tube leading from the tambour connects by means of a rubber tube (inner diameter, 6 mm) to an ordinary open glass funnel (from 30 to 60 mm in diameter), which is placed directly on the patient's chest in the region where the extra sound is best heard, usually near the apex. Equalization of pressure and elimination of the coarse mechanical movements of the wall of the chest are effected by means of an open side tube, connecting the system with the external atmosphere.

All the other mechanical records have been obtained with similar Frank tambours covered with a thin rubber dam, the mirror being placed as in the sound capsule. The side tube, of course, must remain closed for this type of record. The length and caliber of the rubber tubing leading to the different tambours should be uniform. As a source of light for all mechanical records, we used, following the example of Wiggers, a carbon arc lamp with a narrow slit, and a simple optical arrangement for focusing the oblong beam of light on our set of tambours. From each mirror, the recording light ray was reflected on the slit of the camera of the electrocardiograph. The whole system was so placed that the use of prisms was obviated. The half of the film on which the beams played was darkened by means of a shutter between the galvanometer and the camera.

Since all mechanical records were made simultaneously with an electrocardiogram, an extra time marker was unnecessary.

Owing to the difference, however slight, of the angle at which the various beams of light pass through the slit of the camera, simultaneous points on our curves are not necessarily in a straight line vertically one above another. Synchronous points, therefore, have always been carefully checked at each experiment by means of a vertically moving shutter, which instantaneously cuts off or admits

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2 This was recommended to us by Prof. D. J. Edwards.

3 The average weight of our mirrors was about 0.0006 Gm.

the various light beams. Wherever simultaneous points on the various curves are not situated in a vertical line above the electrocardiogram, the deviation is carefully measured and indicated on the tracings.

#### TIME RELATIONSHIP OF THE EXTRA SOUND

By means of these records, then, one can ascertain the exact time relations of the extra sound to other events of the cardiac cycle, and can consider which of such events may have a causal connection with

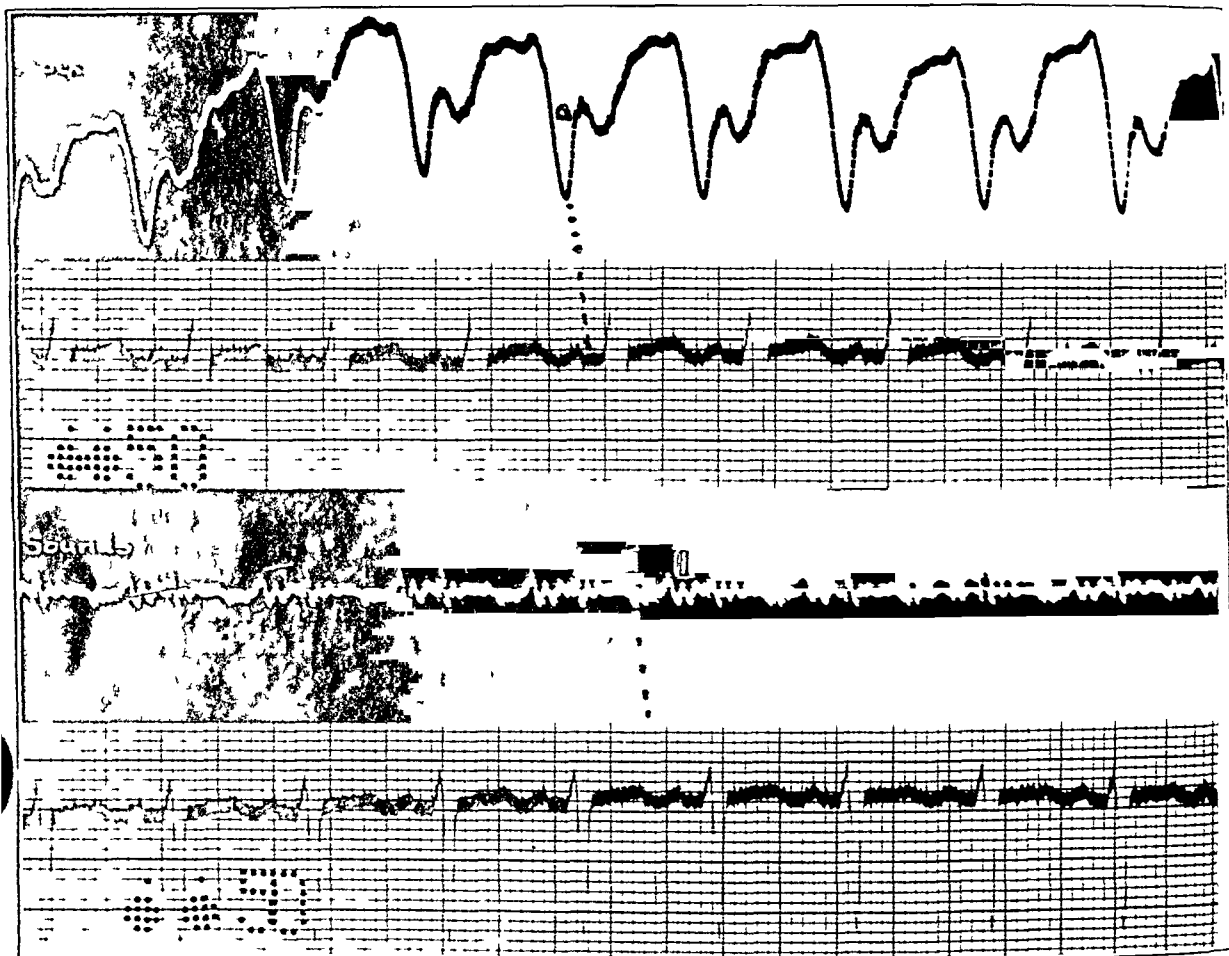


Fig 1—Electrocardiographic record of S S, a man, aged 32, with hypertension and cardiac insufficiency and no murmurs, pulsus alternans and gallop rhythm. The average blood pressure was 200, systolic, 130, diastolic. Upper curve shows the apex beat, with large *a* wave and the lower, sounds. The extra sound is marked III.

the sound. In agreement with all previous observations, in true gallop rhythm the extra sound occurs during ventricular diastole, that is, between the second sound of one heart beat and the first sound of the succeeding cycle. The curves show that this extra sound on the phonocardiogram always occurs at the same time as the latter half of the P wave.

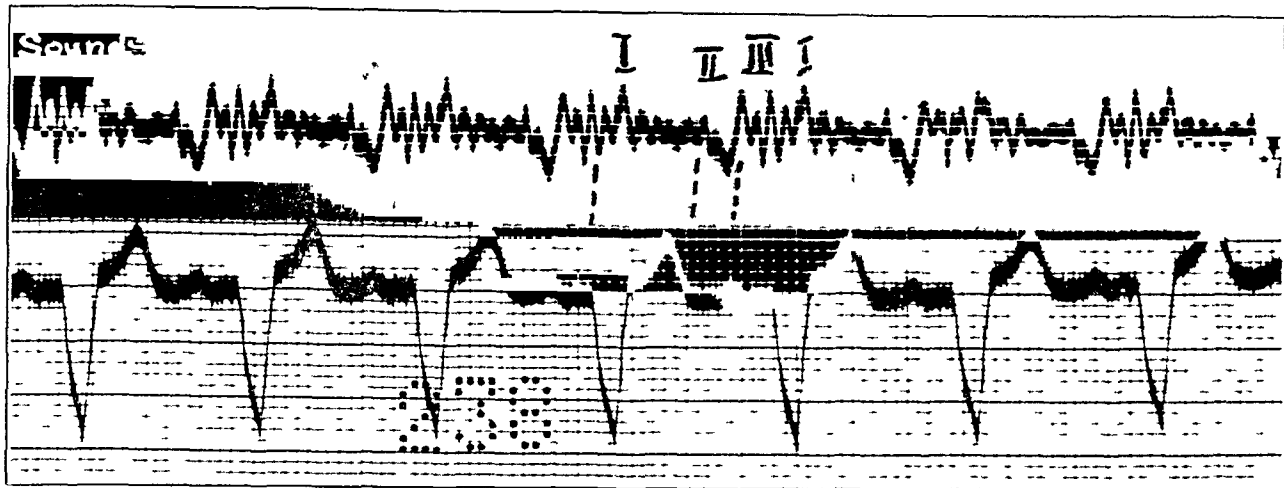


Fig 2—Electrocardiographic record of R K, a woman, aged 63, with coronary disease, hypertension, intraventricular block and gallop rhythm. The average blood pressure was 170, systolic, 110, diastolic. The curves show the third sound simultaneous with auricular contraction.



Fig 3—Electrocardiographic record of Samuel S, a man, aged 38, with chronic nephritis, hypertension, cardiac insufficiency, systolic murmur at the apex and gallop rhythm. The average blood pressure was 250, systolic, 160, diastolic. The upper curve shows the apex beat, with a prominent *a* wave and the lower, jugular pulse and sounds. A loud extra sound is marked III, and occurred simultaneously with auricular contraction.

of the electrocardiogram, and simultaneously with a large distinct wave of the apex beat and the *a* wave of the venous pulse (figs 1, 2 and 3) This would therefore point to the auricular contraction as the determining factor, an idea which was first propounded by Charcelay,<sup>4</sup> in 1838, and which has been frequently reviewed by subsequent authors<sup>5</sup>

The mere observation, however, of the apparent simultaneity of the auricular contraction and the gallop sound cannot be held as satisfactory evidence by itself of a connection between the two events In many cases, a rather marked tachycardia is present, which apparently plays an important rôle in the dynamics of the phenomenon Owing to the increased rate, the diastole is often so short that the extra sound vibrations are crowded in between the preceding second and the following

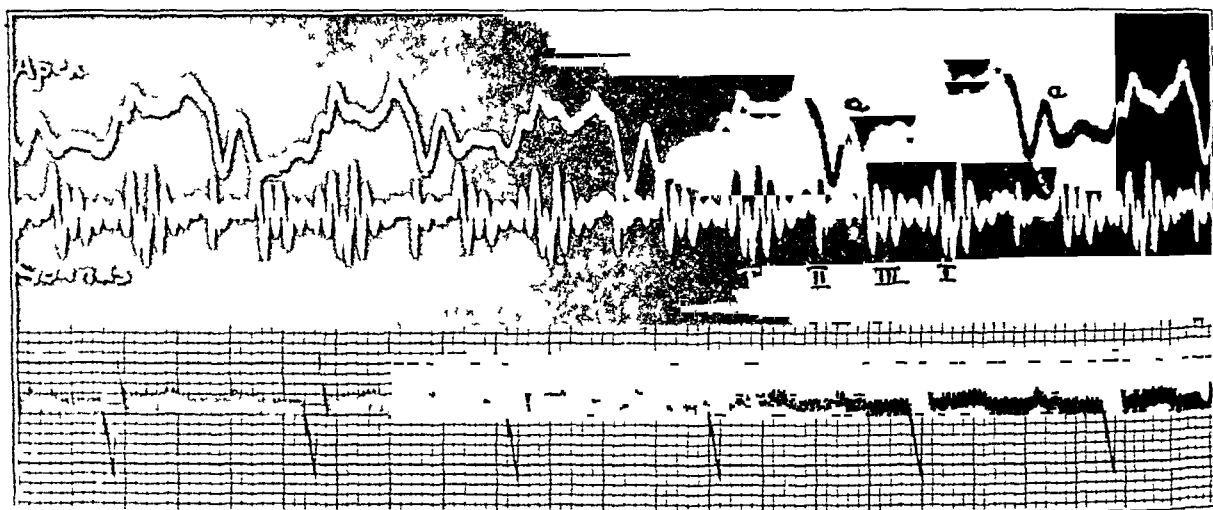


Fig 4—Electrocardiographic record of J. H., a man, aged 54, with hypertension, myocardial insufficiency, partial auriculoventricular block, aortic sclerosis and bronchopneumonia The average blood pressure was 200, systolic, 130, diastolic The extra sound (middle curve) starts 0.06 second after the peak of the P wave The coarse and loud vibrations should be noted In the apex beat (upper curve), the large *a* wave is simultaneous with the third sound It should be noted how the broadening of the apex beat curve makes the *a* wave appear protodiastolic, while the extra sound is clearly middiastolic Simultaneous points of apex and sound records are indicated by dotted lines

first sound thus occupying almost the whole of the period of ventricular diastole It can be argued that because of the shortness of diastole almost any diastolic event must necessarily occur more or less

4 Charcelay Arch gen de med 3 393, 1838

5 Krehl, L Arch f Physiol (Du Bois-Reymond), 1889, p 253 Lewis, Thomas Lectures on the Heart 1915, p 66 Muller, Friedrich Munchen med Wchenschr 53 786, 1906 Robinson, Canby Am J M Sc 135 670, 1908

simultaneously with auricular contraction. This difficulty, however, vanishes in cases showing partial auriculoventricular block, in which, because of a prolonged P-R interval, the groups of sound oscillations are separated from each other more definitely. One such case is shown in figure 4. The extra sound here forms a large group of vibrations, which are even more intense than those of the second sound, and are clearly related to the P wave in the electrocardiogram. This record, in conjunction with the previous observations, seems to us convincing proof that auricular contraction and gallop sound are indeed connected, since it is clear that shifting of the auricular contraction from its usual place in diastole is accompanied by shifting of the third sound. The measurement of the time relations shows that the extra sound in this case starts at an average time of 0.05 second after the onset of the P wave in the electrocardiogram, while the first sound has approximately

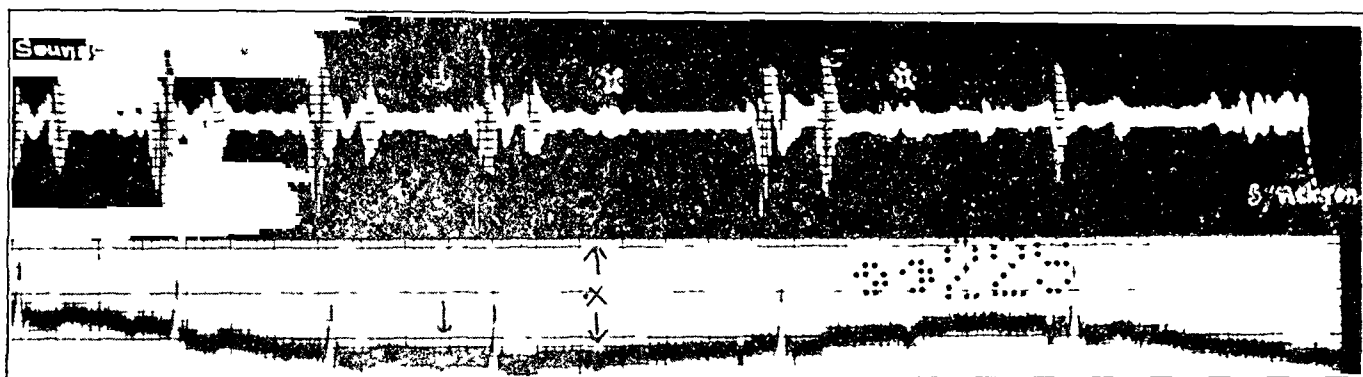


Fig 5—Electrocardiographic record of H. A., a man, aged 23, with mitral stenosis and insufficiency and presystolic and systolic murmur at the apex. It should be noted that the presystolic murmur shifts its place in diastole in the same sense as auricular contraction. When the auricular stimulus is blocked from reaching the ventricle (\*) the murmur is recorded, isolated in early diastole.

the same time relation to the beginning of the QRS complex (0.06 second).

A similar situation may be found in so-called presystolic murmurs of mitral stenosis. Here, also, it is known that the murmur may change its position in diastole along with the auricular contraction. An interesting example of this behavior is given by a curve (fig 5) taken of a patient with combined mitral and tricuspid lesions. The patient suffered from short attacks of paroxysmal disturbances of conduction. On the one record, the murmur may be seen to be presystolic when auriculoventricular conduction is adequate, middiastolic, when the P-R interval is lengthened, and protodiastolic, when conduction fails, the ventricular complex is skipped and the P wave remains isolated during a long pause.



## PROTODIASTOLIC AND PRESYSTOLIC GALLOP RHYTHM

As far as is shown by the records, it would appear that—at least in the hypertensive group of cases showing gallop rhythm—the distinction between protodiastolic and presystolic gallop is not of great significance.<sup>6</sup> Granting that in these cases gallop sound and auricular contraction are interrelated, it will depend entirely on the relative position of auricular contraction between the preceding second and the subsequent first sound whether the gallop is protodiastolic or presystolic. The factors determining this are, therefore, the rate of the heart beat, on the one hand, and the length of the auriculoventricular conduction interval, on the other.

1 *Rate*—The shorter the diastole becomes with increasing rate, the nearer the extra sound approaches the preceding second sound. At a relatively slow rate, it is presystolic, at a higher rate, middiastolic, and it may even become protodiastolic, when with mounting tachycardia the interval between the end of the preceding systole and the next auricular contraction becomes shorter than the interval between the latter and the following first sound.

2 *Auriculoventricular Conduction Time*—Just as changes of rate by mere shortening of diastole may diminish the interval between ventricular systole and the next auricular contraction, so may disturbances in conduction produce the same effect by lengthening the interval after which ventricular contraction follows auricular contraction. With increasing delay in conduction, the type of the gallop rhythm will again be changed from presystolic through middiastolic to protodiastolic. The case shown in figure 4 is of this type. That protodiastolic gallop may be due to prolongation of the auriculoventricular interval has already been suggested by Gallavardin,<sup>7</sup> on the basis of a similar case, in which, however, sound curves were not obtained. Here it may be remarked that although higher degrees of block are not common in gallop rhythm,<sup>8</sup> simple prolongations of the P-R interval are not infrequent, conduction time ranges generally about the upper limit of normal (0.2 second).

Quite aside from these considerations, it must be remembered that the clinical determination of the character of the gallop—whether protodiastolic or presystolic—becomes increasingly difficult with increasing rates. Even on the sound records it is sometimes hard to determine

6 Müller (footnote 5, third reference)

7 Gallavardin, L. *Arch. d. mal. du coeur* 12 410, 1920

8 White, Paul D. Clinical Significance of Gallop Rhythm, *Arch. Int. Med.* 41 1 (Jan.) 1928

(fig 2), in fact, Potain himself, who originated the distinction, admitted that clinically it is often impossible to differentiate between the types.<sup>9</sup> The attempt at differentiation has nevertheless remained a favorite pastime in bedside medicine, in spite of its difficulty, perhaps because of it

#### RECORDS OF THE APEX BEAT

A large diastolic wave in the records of the apex beat has been described frequently. Muller,<sup>6</sup> Canby, Robinson<sup>10</sup> and others have assumed that in presystolic gallop this wave is an expression of auricular contraction. In fact, it has hitherto been almost the only graphic evidence of a connection between the accessory sound and auricular contraction. Our records of gallop rhythm (figs 1, 3 and 4) demonstrate beyond doubt the simultaneity of this wave, the third sound and auricular contraction. The wave shows, moreover, the same variable

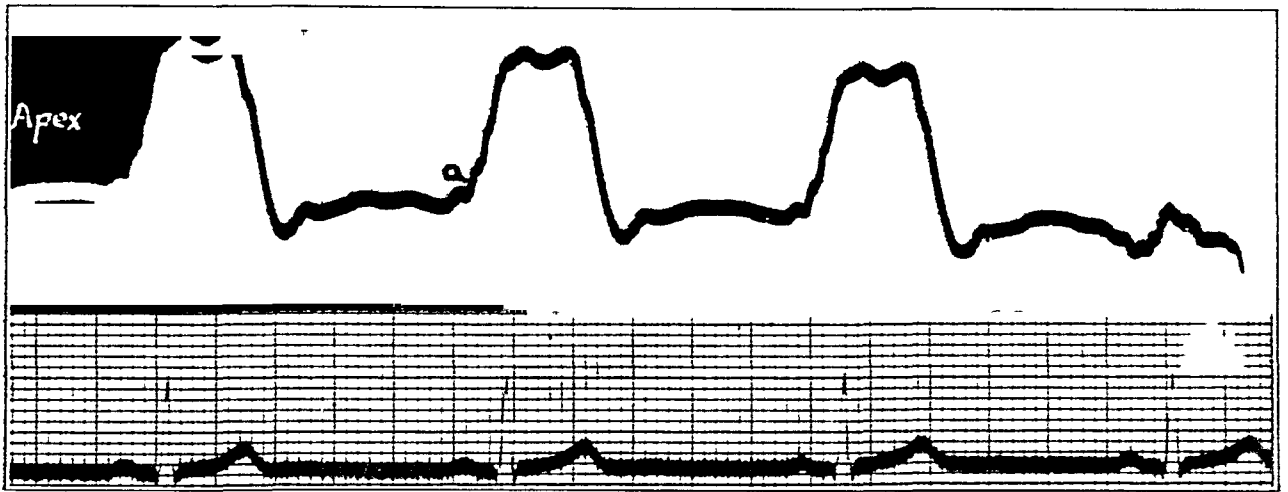


Fig 6—Electrocardiographic record of H. H., a man with mitral insufficiency. Normal electrocardiogram. Normal apex beat, showing the small and insignificant normal *a* wave.

position in diastole as has already been demonstrated for the extra sound. The large size of this auricular wave in gallop rhythm is remarkable, and it was constantly observed in all our cases. It must be kept in mind that the *a* wave of the normal apex beat is small, often scarcely visible (fig 6).

In connection with the use of the apex beat as a means of locating the auricular contraction, there is one source of error which has hitherto escaped attention. Owing to the slow rate at which relaxation proceeds in these cases, the pressure curve is markedly widened. Hence the *a* wave of the apex beat curve may follow the downstroke so quickly as to appear protodiastolic even though it is actually middiastolic as

9 Potain C. *L'union medicale* 1875 vol 20, p 706

10 Robinson (footnote 5, fourth reference)

shown by the sound record. Figure 4 is an interesting example of such a case. This contrast between apex beat and sound records as regards the apparent location of the extra sound in diastole becomes more important if one considers that the majority of authors have relied almost entirely on records of the apex beat.

#### ACCESSORY SOUNDS OF OTHER TYPES

The classic form of gallop rhythm, that observed in hypertensive disease, therefore, is characterized by a third sound occurring simultaneously with auricular contraction. As the term "gallop" has often been used rather loosely to describe almost any third sound appearing in diastole, it seems worth while to mention briefly certain types of extra



Fig 7—Electrocardiographic record of a man, aged 23, with systolic murmur at the apex but no diastolic murmur. The roentgenographic appearance of the heart, the blood pressure and the electrocardiogram were normal. The sound record shows a typical physiologic third heart sound.

sounds with a definite difference in mechanism. We distinguish two main groups:

1. The physiologic third heart sound has been described by many modern writers (Gibson,<sup>11</sup> Einthoven,<sup>12</sup> Thayer,<sup>13</sup> and Hirschfelder<sup>14</sup>), but satisfactory evidence as to its origin is not yet available. A glance at a record (fig 7) however convinces one that auricular contraction at least is not responsible for it, the mechanism is certainly not the

11 Gibson, A. I. *Lancet* 2:1380, 1907.

12 Einthoven, W. *Arch. d. Ges. Physiol.* 120:31, 1907.

13 Thayer, W. S. *Boston M. & S. J.* 158:713, 1908.

14 Hirschfelder, A. D. *Diseases of the Heart and Aorta*, Philadelphia, J. B. Lippincott Co., 1918, p. 173.

same as that of gallop rhythm in hypertension. According to Bridgeman,<sup>15</sup> the sound occurs generally 0.47 second after the onset of the anacrotic wave of the apex beat. The same author suggests vibrations of the auriculoventricular valves as a possible cause, while Einthoven<sup>12</sup> located the point of origin in the aorta or aortic valves. There is not, however, definite proof of either of these assumptions.

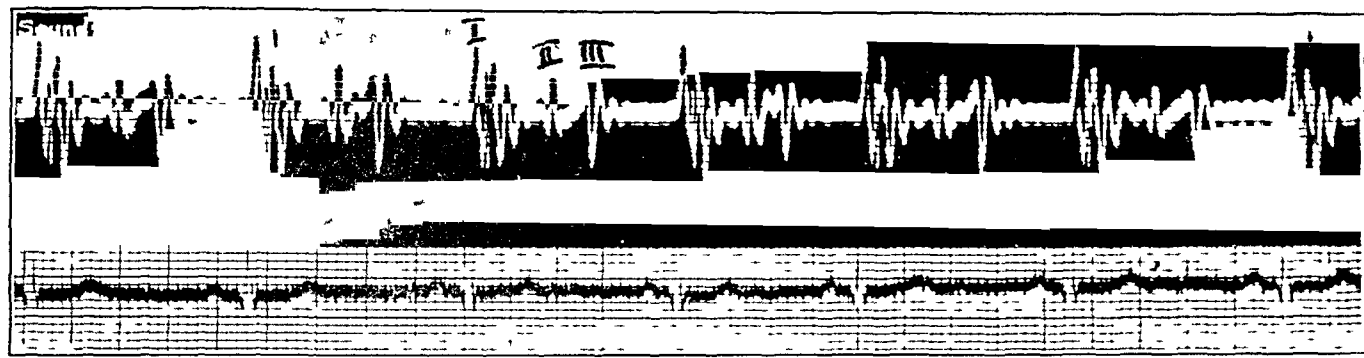


Fig 8—Electrocardiographic record of N. W., a boy, aged 16 years, with rheumatic fever, mitral insufficiency and stenosis. The blood pressure was 104, systolic, 60, diastolic. The group of oscillations marked III represent a "sound-like" diastolic murmur. At other periods, the patient showed an ordinary diastolic rumble.

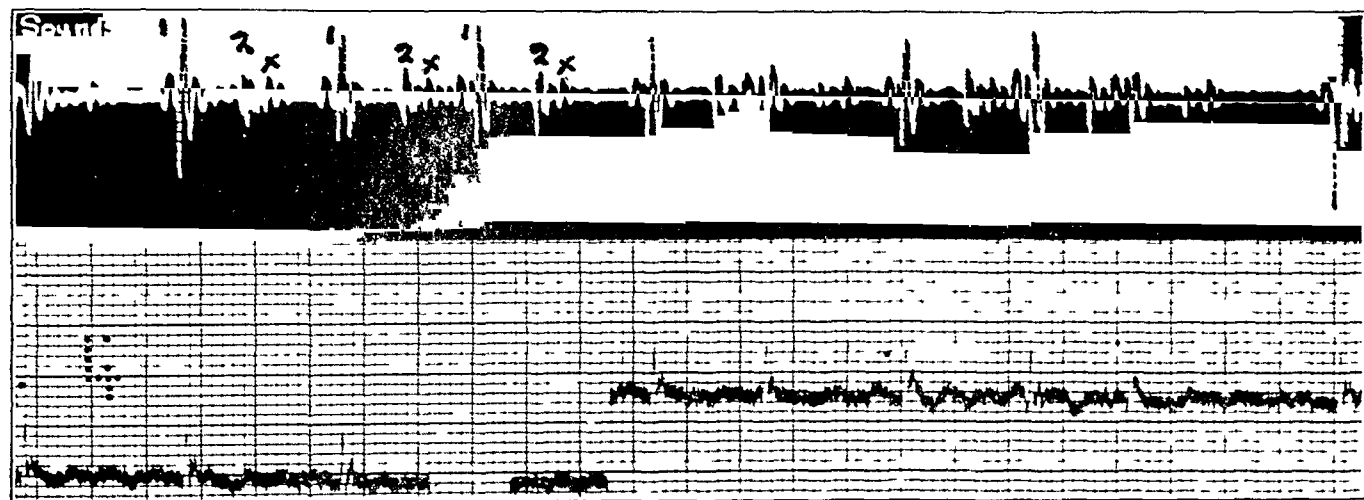


Fig 9—Electrocardiographic record of B. L., a woman, aged 39, with mitral stenosis and auricular fibrillation. The record shows reduplication of the second sound.

2 The so-called reduplication of the second sound in mitral stenosis (the *claquement mitral* of the French authors) is better known. It may be a rudimentary murmur or the initial phase of a diastolic murmur associated with the opening of the rigid mitral valves in early diastole (fig 8). It is certainly independent of auricular contraction since it often occurs in cases showing auricular fibrillation. Figure 9 shows

15 Bridgeman, E. W. *Heart* 6:41, 1915.

a reduplicated second sound in a patient with mitral stenosis with auricular fibrillation. On the other hand, we have never observed a typical gallop sound in hypertensive cases showing auricular fibrillation, which is in accordance with the observation of Lewis<sup>16</sup> that presystolic gallop disappears in auricular fibrillation.

Both of these types of accessory sounds are easily distinguished clinically from gallop rhythm. They both lack the peculiar tactile character of the gallop sound with its soft, diffuse shock, which often makes it felt rather than heard.<sup>17</sup>

#### MECHANISM OF GALLOP RHYTHM

In the group of cases investigated—all showing hypertensive cardiac insufficiency—we have satisfied ourselves that auricular contraction and the extra sound are simultaneous. While our records show this fact unequivocally, the view that an audible auricular contraction is responsible for gallop rhythm is by no means a new one. In fact, Charcelay,<sup>4</sup> the first observer who gave a lucid description of the phenomenon advanced this theory as long ago as 1838, assuming that the contraction of a hypertrophied auricle might occasionally become audible. Although he did not use the expression "gallop," there is no doubt that this is what he was describing. We do not intend to attempt a complete survey of the immense volume of literature on gallop rhythm, more particularly as a review on the subject was published last year by Holt.<sup>18</sup> In passing we might mention that Charcelay's view found little acceptance in the subsequent decades and was in turn replaced by such theories as those of asynchronism,<sup>19</sup> polysystole,<sup>20</sup> active dilatation in diastole,<sup>21</sup> and contraction of papillary muscles.<sup>22</sup> Potain<sup>9</sup> was the first to distinguish between protodiastolic and presystolic gallop rhythm. According to him the main factor is a rigid, fibrosed ventricle which must be forcibly distended by the inflowing blood. It is this sudden distention of the rigid muscular wall which in his opinion, leads to the production of the third sound. In his theory, the rôle of the auricular contraction is neglected, whenever the blood flow suddenly distends the ventricle during diastole the sound will occur. This, of course, fitted well into Potain's principle distinction between protodiastolic and presystolic gallop rhythm. More recently, the theory of auricular origin was again

16 Lewis (footnote 5, second reference)

17 Potain, C. *Semaine med* 20 175 1900

18 Holt E. *Am Heart J* 2 453 1927

19 Bouveret L. and Chaballier. *Lyons med* 60 241, 1889

20 D'Espine. *Rev de med* 1 117 1882

21 Brauer. *Verhandl d Kong f inn Med* 21 189, 1904

22 Chauveau A. *These de Paris* 1902 no 315

taken up by George Johnson<sup>23</sup> and later by Muller,<sup>6</sup> Canby Robinson<sup>10</sup> and Laubry and Pezzi<sup>24</sup>. All these authors, however, maintain the distinction between protodiastolic and presystolic gallop.

In our opinion, however, this distinction is of value only if two different types of mechanism are designated. As has been stated a mere variation in the length of diastole may so alter the relation of the third to the preceding second and the following first sound as to produce either of these types of gallop. The distinction apparently loses its significance if the same mechanism can in one instance produce protodiastolic, and in the next presystolic, gallop rhythm, just because the sinus rate happens to be different in the two cases. If, however, protodiastolic gallop should prove to be due to an essentially different mechanism, the distinction between this and presystolic gallop would be of great importance. According to Canby Robinson and others, protodiastolic gallop corresponds to an exaggerated "physiologic" third sound, while the typical presystolic gallop is due to an audible auricular contraction—two radically different mechanisms.

The physiologic third sound, whatever may be its origin, whether it is due to vibrations of the auriculoventricular valves in early diastole or to some other mechanism, is not due to an active contraction of any part of the heart. It is most frequently and almost exclusively found in young persons, it varies with the position of the patient, and it is rarely heard in the broad chested type of patient, who so often shows gallop rhythm. Occasionally the physiologic third sound is loud and exaggerated, but here the exaggeration has by no means the ominous significance of gallop rhythm.

The situation is entirely different with those hearts which exhibit audible auricular sounds. All our cases of gallop rhythm suggested this type of mechanism and, in contrast to the preceding group, presented definite evidence of heart failure.

The conditions under which auricular contractions become audible are apparently definitely abnormal. This leads to the questions

- 1 Why is auricular contraction not heard under normal conditions?
- 2 What are the conditions that make auricular systole an audible event?

The fact that the normal auricular contraction is inaudible certainly needs explanation. That the mass of muscle is not too small to produce a sound is shown by Krehl's<sup>25</sup> observation that auricular sounds occasionally become audible in the heart of a dying dog, when heard, they are weaker than the ventricular sounds but are definitely perceptible.

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23 Johnson, George. *Lancet* 1 697, 1876

24 Laubry and Pezzi. *Bruit de Galop*, Paris, 1927

25 Krehl (footnote 5, first reference)

The idea that auricular and first ventricular sounds fuse into one under physiologic conditions is not tenable. The interval between the occurrence of the two sounds is undoubtedly long enough for the recognition of two distinct entities, since acoustic vibrations separated from each other by an interval of even so little as 0.01 second can be perceived as two distinguishable sounds. There seems to be no reason why auricular contraction should not normally be heard unless there are factors causing the sound vibrations to be damped. This, we believe, is what actually occurs. In 1911, von Wyss<sup>26</sup> and later Bridgeman,<sup>27</sup> by means of excellent curves, showed that phonocardiographic records of normal persons occasionally present a small group of vibrations occurring at an interval of 0.07 second before the first sound.<sup>28</sup> These vibrations are evidently highly damped, as shown by their small excursions, which diminish so rapidly that often only a single wave is seen. This marked damping apparently depresses the vibrations below the level of audibility. It is not difficult to see that the chief factor in the production of damping effects must be the ventricle. In the normal heart the ventricle is completely relaxed when auricular contraction occurs, its walls forming a soft, flexible mass which yields readily to the slightest pressure of the inflowing blood. In this phase auricle and ventricle form one large cavity, whereof the soft ventricular portion not only fails to participate in the vibrations of the auricle, but acts as a damper that silences whatever vibrations may have been started by the sudden contraction of the auricle muscle fibers. The amount of damping is clearly proportional to this yielding capacity of the normal ventricular muscle in diastole. With rising tension of the ventricular wall, the damping influence must be diminished and the chances of audibility improved. Bridgeman<sup>27</sup> has already suggested that a slightly higher ventricular tension in his cases might account for the occurrence of presystolic sound waves on the curves.

Here we find ourselves in the midst of the central problem already referred to. What are the circumstances in which auricular contraction becomes audible?

As long as the damping action of the ventricle is preserved, auricular contraction remains inaudible. If, however, the ventricle has lost its silencing power the reason for this change can only be an alteration in the state of its wall. We must assume that the ventricular wall is

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<sup>26</sup> Von Wyss. *Deutsches Arch f klin Med* **101** 1, 1911.

<sup>27</sup> Bridgeman, E. W. Notes on a Normal, Presystolic Sound, *Arch Int Med* **14** 476 (Oct) 1914.

<sup>28</sup> Einthoven's paper on the physiologic third heart sound contains a sound record with characteristic presystolic vibrations (*Arch f d ges Physiol* **120** 31, 1907 fig 5, table 1). The oscillations are small and damped, and have the same relation to the following first sound as in Bridgeman's cases.

no longer in a state of complete relaxation in diastole, but now offers a marked resistance to the entrance of blood during auricular systole. The pressure wave produced by the contracting auricle meets with a ventricular wall which no longer yields passively to every impulse, the pressure is raised suddenly in the large common cavity comprising both auricle and ventricle, and the whole of its surrounding wall is thrown into transverse vibrations. These, transmitted to the wall of the chest, are heard as the familiar third sound of gallop rhythm. As has often been stated, it is best heard near the apex, which is that portion of the vibrating muscle mass closest to the wall of the chest. In this conception, the extra sound is a combined auricular and ventricular effect, and the participation of the ventricle explains why a sound, auricular in origin, should be so well perceived over the ventricle.

This explanation involves two assumptions, first, an altered condition of the ventricular muscle, and second, an increased pressure in the auricle. Is there any evidence, experimental or otherwise, that would support the hypothesis that these changes are likely to occur under conditions of hypertension with cardiac insufficiency?

At first it seems paradoxical to suppose that a failing heart, which is commonly associated with a "weak" musculature, should present a ventricle of which the fibers are at an augmented tension. However, the experimental work of Frank,<sup>29</sup> Patterson, Piper and Starling,<sup>30</sup> Straub<sup>31</sup> and others has taught us that under certain experimental conditions this is actually the case. The dynamics of the heart working under increased resistance were first studied by Frank. In his well known investigations on the heart of the frog, he showed that the diastolic tension of the heart muscle determines the efficiency of the contraction. Hence a rise of peripheral resistance, which would of itself diminish the output, causes an increased initial diastolic tension that, by producing a stronger contraction, enables the heart to maintain its stroke volume. This mechanism of compensation, however, works only within certain limits, if the peripheral resistance rises beyond a certain critical point, then a further increase of diastolic tension fails to evoke a stronger contraction, on the contrary, the efficiency of the contraction diminishes, the stroke volume falls and insufficiency sets in.

Starling and his collaborators and later Straub, working with Starling's heart-lung preparation, were able to show that essentially the same mechanism prevails in the mammalian heart. As an illustration,

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29 Frank, O. *Ztschr f Biol* **32** 370, 1895

30 Patterson, S. W., Piper, H., and Starling, E. H. *J Physiol* **48** 465, 1914

31 Straub, H., in Bethe, A., et al. *Handbuch der Normalen und pathologischen Physiologie*, Berlin, Julius Springer, 1928, vol 7 p 254



we reproduce curves from Straub's work<sup>31</sup> (fig 10) recording the pressures in the left ventricle (upper group) and the left auricle (lower group) during an experiment with increasing arterial load. Curves 1, 2 and 3 show the pressures while the heart action is still efficient. One can observe the gradually increasing diastolic tension accompanied by a corresponding rise of systolic pressure. The systolic pressure curve is little widened. With the onset of insufficiency, however (curve 4), the diastolic tension still continues to rise, but the systolic pressure falls, and the widening of the curve becomes marked. For our purposes it is particularly interesting to note the behavior of the auricular pressure. At first during the stage of compensation, the pressure level rises

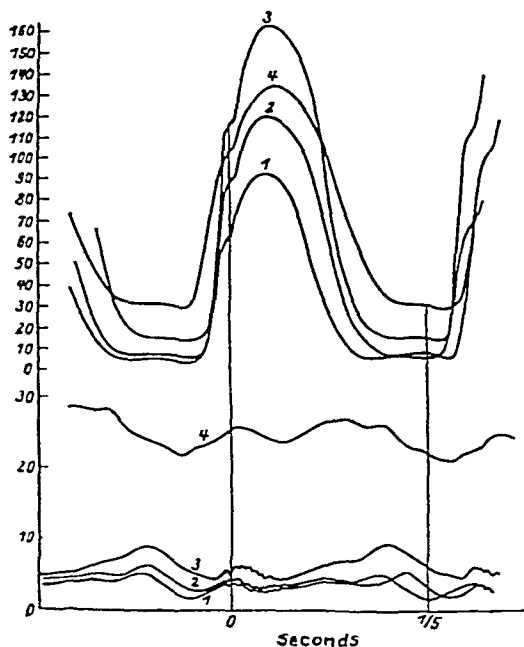


Fig 10—After Straub. The curves show the changes of intraventricular (upper series) and intra-auricular (lower series) pressure, during an experiment with increasing arterial load. The gradual increase of diastolic tension, particularly when the stage of insufficiency is reached (curve 4), should be noted. The intra-auricular pressure is likewise driven up at the same time.

but little and gradually, but as soon as the stage of insufficiency is reached (curve 4), the intra-auricular pressure rises abruptly to a considerable height.

One may therefore reasonably assume that the dynamics of cardiac insufficiency in human hypertension are basically of a similar nature. Both factors which we postulated for the production of gallop rhythm are at least made probable by the experimental work. The conception explains at once the prevalence of gallop rhythm in hypertensive cases with cardiac insufficiency, while the inconstancy of its occurrence follows from the functional nature of the phenomenon. It is often reported

that with recurring compensation the extra sound may disappear. Its production is the result of a functional process and does not depend, as in the original hypothesis of Potain, on a rigid fibrosis of the ventricle.

This conception of the mechanism of gallop rhythm supplies a natural explanation of other peculiarities connected with the phenomenon, particularly the constant finding of a large auricular wave in the apex beat, which is paralleled in the high auricular pressure in Straub's experiment.

The main condition, then, for the establishment of gallop rhythm is an increased diastolic tension of the ventricular muscle fiber, which may be present even before the appearance of the usual clinical signs of cardiac insufficiency. White<sup>8</sup> showed, however, that congestive heart failure was present in a majority of his cases, at least 61 per cent showing symptoms of cardiac insufficiency. White also made the observation that an

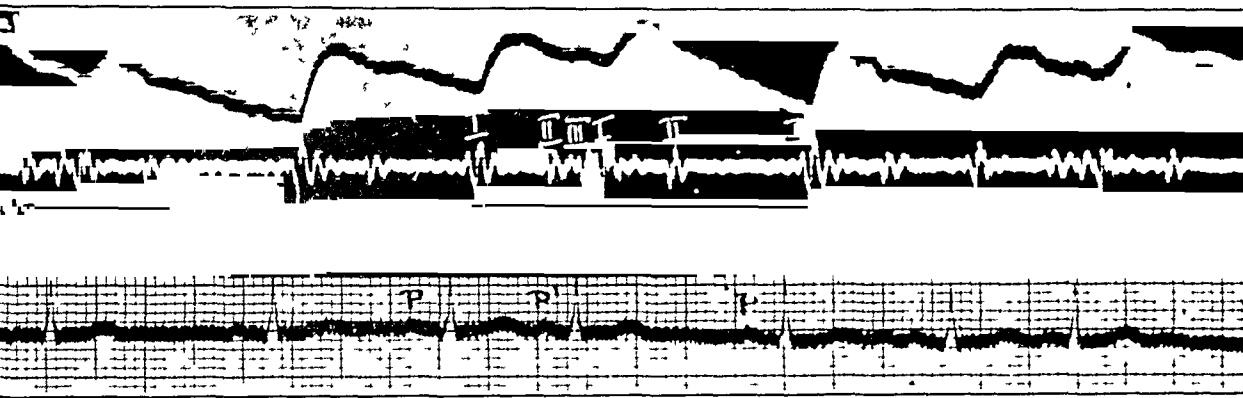


Fig 11—Electrocardiographic record of B. M., a woman, aged 53, with bronchial asthma, tuberculosis and hypertension. The record shows coarse vibrations corresponding only to those auricular contractions which are premature. The normal auricular contractions remain silent. The audibility of the auricular extrasystoles is perhaps favored by the patient's hypertension.

improvement in the clinical syndrome of heart failure under digitalis therapy was occasionally accompanied by the disappearance of the extra sound. This agrees with our own observation that gallop rhythm is not infrequently a temporary phenomenon, which is determined by the functional state of the muscle. Any cause, whether permanent or temporary, which changes the state of the ventricular muscle fibers to a heightened tension is likely to produce audible auricular sounds. A case in which auricular extrasystoles occur in early diastole might illustrate this fact (fig 11). Here the extrasystoles frequently occur at an interval of about 0.06 second after the end of the second sound and therefore probably at a time when the ventricle is not yet fully relaxed. Consequently, the usual damping effect of the ventricle being eliminated, a group of vibrations appear in the sound curve simultane-

ously with the premature P wave of the electrocardiogram. This is the more interesting, since in the normal cycles of the same patient auricular contraction remains silent. We have already mentioned that tachycardia, with its shortened diastole, favors the production of gallop rhythm.

In this connection it may be recalled that auricular sounds are often heard in cases showing complete auriculoventricular heart block, in which the conditions for their audibility are particularly favorable. The loss of coordination between auricular and ventricular rhythms causes the auricle frequently to beat against a contracting, or only partially relaxed, ventricle thus increasing the resistance to auricular contraction. This in turn tends to increase the force of auricular contraction. Other favorable factors are the frequently present hypertension, the large diastolic filling of the ventricle and its increased diastolic tension. Figure 12 illustrates such auricular sounds in complete heart block.

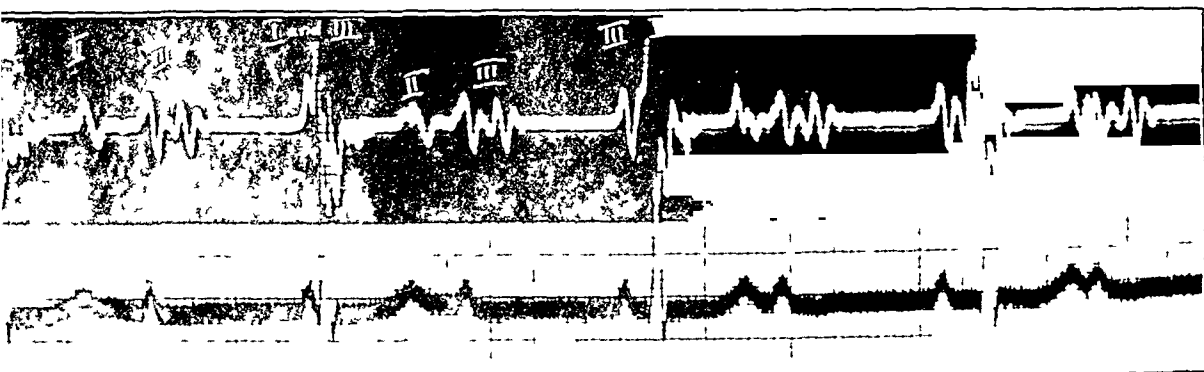


Fig 12—Electrocardiographic record of H. L., a man, aged 60, with complete auriculoventricular block, following rheumatic infection. An empyema complicating left-sided pneumonia necessitated the resection of a number of ribs, in this way a large portion of the heart was exposed, which remained merely covered with skin. The sound records are taken from the apex, and show the large, coarse vibrations accompanying auricular contraction.

It may be well to point out here that the auricular sounds in dissociation have exactly the same peculiar "palpable" quality as the extra sound in gallop rhythm. This curious tactile component of the gallop sound has been emphasized by many observers since its first classic presentation by Potain<sup>17</sup>. He described the accessory sound as dull and as "felt" rather than heard by the ear. This is the reason why it can be best perceived with the wooden stethoscope. The impulse can often be felt by hand on the precordium. This description of gallop sounds is exactly applicable to the case of auricular sounds in complete block, and this close resemblance is, in our opinion, an important additional argument in favor of the auricular origin of the accessory sound in gallop rhythm.

It is not necessary to look far for an explanation of the dull character of the sound. First a valvular component does not enter into the

production of the "bruit de galop", it is a pure muscular sound. Then the cavity in which it originates is large, comprising both auricle and ventricle and thus tending to produce vibrations of a rather low frequency. Finally, the onrush of blood into the ventricle accelerated by the auricular contraction adds to the "palpable" character of the phenomenon.

#### SUMMARY

1 Gallop rhythm as seen in persons with hypertensive disease is produced by an extra sound simultaneous with auricular contraction.

2 Increased diastolic tension of the ventricle and increased intra-auricular pressure are regarded as the main factors in the causation of the accessory sound.

3 The relation of these conditions to the theory of cardiac insufficiency is discussed.

4 Protodiastolic and presystolic gallop rhythm, in the hypertensive type of case, are due to essentially the same mechanism.

5 The physiologic third sound and the reduplication of the second sound are distinguished from true gallop sound because they are produced by fundamentally different mechanisms.

# EXPERIMENTAL HEART BLOCK

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AND

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In the course of our experimental work on the heart, a new method was devised for increasing the intra-auricular and intraventricular pressures of the intact dog. This was done by tying a balloon on the tip of a properly bent glass rod (2 mm in diameter) and inserting the rod into the right auricle or ventricle by way of the right jugular and innominate veins. This apparatus was connected with a mercury manometer and a pressure bottle which permitted raising the intra-auricular pressure to any desired amount. It was found unnecessary to use heparin to prevent coagulation, as clotting of blood was observed only once in twenty-five experiments. After a few trials, we were able to put the balloon into the right auricle, the right ventricle and the inferior or superior vena cavae at will. Control electrocardiograms were taken before and after tracheotomy, after tying the right jugular vein, after inserting the balloon and during the experiment after sectioning both vagi. Ether anesthesia was used.

## RESULTS

With an intra-auricular pressure of from 15 to 60 mm of mercury, there was gradual lengthening of the PR interval from 0.08 second to 0.2 second, a period of 2:1 block, establishment of an independent ventricular rhythm and finally complete suppression of the P wave.

After release of the pressure in the balloon, there was a gradual return to the control type of sinus rhythm with normal PR intervals.

This procedure was repeated three times with the same results in one dog and similar observations were made on seven different dogs. These results were produced in one of three ways: (1) by mechanical pressure, (2) by anemia or (3) by a combination of mechanical pressure and anemia.

We were unable to obtain any similar results by placing the balloon entirely within the right ventricle or the inferior or superior vena cavae nor could we obtain such results in experimental pericardial effusion, or in open chest operations in which the coronary sinus or the circumflex branch of the right coronary artery was tied. Double vagotomy did not have any effect on the results when done during the block produced with this method, nor did it prevent the appearance of the block.

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\* Submitted for publication Sept. 10, 1928.

\* From the Department of Medicine of Rush Medical College, University of Chicago.

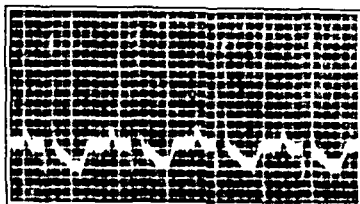


Chart 1—Control after balloon was inserted into right auricle PR 0 09 sec, PP 0 36 sec

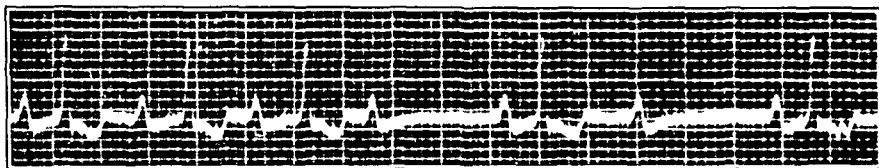


Chart 2—Intra-auricular pressure increased, showing PR 0 21 sec, PP 0 51 sec, two to one block

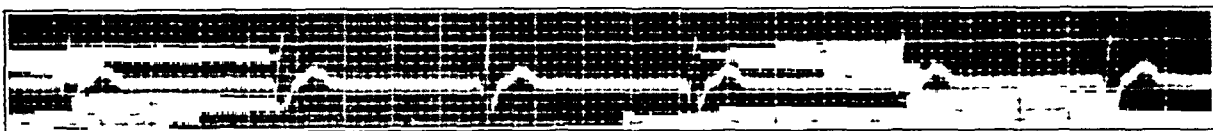


Chart 3—Complete suppression of P wave with establishment of ventricular rhythm RR 0 86 sec

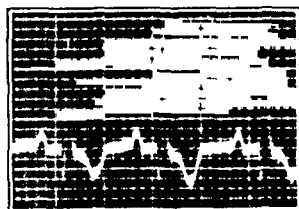


Chart 4—Recovery after pressure in balloon was released PR 0 10 sec, PP 0 40 sec All tracings are of lead I, time markings at one twenty-fifth second intervals

## CONCLUSIONS

- 1 The PR interval was gradually prolonged into 2 1 and into complete block
- 2 The rate of the sinus node was depressed
- 3 Complete suppression of the sinus node was produced

# THE EXCURSION OF THE COSTAL MARGINS IN HEALTH AND IN DISEASE\*

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AND

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RAY PROOK, M D

Between 1913 and 1926, C F Hoover of Cleveland published a number of interesting articles on the mechanics of respiration in which he emphasized the diagnostic significance of the movements of the costal margins. According to this author, the intercostal muscles and the diaphragm have antagonistic actions. The intercostals enlarge the transverse and anteroposterior diameter of the lower part of the thorax in inspiration, and tend to draw the costal margins away from the median line and to widen the subcostal angle, while the contraction of the diaphragm increases the longitudinal diameter of the chest and at the same time tends to draw the costal margins toward the median line, thus narrowing the angle between them. The extent and direction of the marginal motion are thus the result of the antagonistic forces exerted by the intercostal muscles and the diaphragm.

Hoover further claimed, however, that when the arch of the diaphragm is flattened from any cause, such as a pleural effusion, the muscle is placed at a mechanical advantage which gives it mastery over the intercostals as shown by the narrowing of the subcostal angle in inspiration, while if the convexity of the diaphragm is increased, as by a subphrenic abscess, the action of the muscle on the costal margin becomes less effective; the intercostals control the situation and the inspiratory effort causes flaring of the lower ribs with increase of the subcostal angle. To quote Hoover's words: "there is exhibited in the costal border movements a very accurate index of the balance of power between diaphragm and intercostals"<sup>1</sup>. Again, "The movement of the costal borders is a reliable index of the elevation or depression of the arch of the diaphragm"<sup>2</sup>.

From all this it follows that careful observation of the marginal movements during inspiration will give valuable information about the condition of the diaphragm, and will enable the physician to draw important inferences therefrom. As Hoover said: "Such studies improve the accuracy with which one differentiates between infraphrenic and supra-

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\* Submitted for publication Oct 1 1928

\* From the New York State Hospital for Incipient Pulmonary Tuberculosis

1 Hoover, C F The Importance of the Patient's Position in Studying Lung Excursion, J A M A 81 1602 (Nov 10) 1923

2 Hoover, C F The Functions of the Intercostal Muscles, J A M A 73 17 (July 5) 1919



phrenic disease and enables one to differentiate between lesions which cause phrenic displacement and those which do not modify the plane of the diaphragm"<sup>3</sup>

In brief, Hoover thought that an inward movement of the costal margin during inspiration indicates either flattening or increased "activation" of the diaphragm, while an outward movement means that the surface of the diaphragm is convex, or that its activation is diminished relative to the intercostals. These modifications of the marginal motion constitute the so-called "Hoover's sign."

Considerable controversy has arisen regarding the validity of Hoover's conclusions and the importance of his "sign," and we were prompted to make a reappraisal of his views in so far as they apply to disease of the lungs and pleura.

We have been unable to establish any criteria of the degree of activation of the diaphragm aside from the amplitude of its excursion. Further, we have been unable to detect any such constant relationship between the position and contour of the diaphragm and the excursion of the costal margins as Hoover claimed.

Our observations lead us to the conclusion that the particular type of breathing (abdominal, lower thoracic, upper thoracic) and the lateral sway of the thorax, which often occurs during respiration, are more important in determining the direction of the costal excursion than are the position and contour of the diaphragm.

#### THE EXCURSION OF THE COSTAL MARGINS IN HEALTH

The movements of the costal margins were first studied in the healthy subject, and these observations were used as a basis to interpret their variations in disease. Seventy-one subjects were studied, forty males and thirty-one females, ranging between the ages of 18 and 40. Subjects presenting conditions which might modify the costal excursion, such as evident deformity of the chest, were excluded from the series. Observations were made during quiet, moderate and forcible breathing, in the standing, sitting and supine positions, and care was taken that the subject was relaxed at the time the observations were made.

In some healthy persons the thorax is slightly asymmetrical and the two sides of the chest expand unequally during inspiration. Of course, in these cases the costal margins reveal similar inequalities in their excursion since they are an integral part of the thorax and of necessity share in its movements.

Lateral flexion of the thorax during deep inspiration may cause marked inequality in the movement of the costal margins. The move-

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3 Hoover C F Diagnostic Significance of Inspiratory Movements of the Costal Margins, *Am J M Sc* **159** 633 (May) 1920

ment of the costal margin on the flexed side is limited or may even be inward, while there is a heaving motion of the opposite side, and its margin flares in an exaggerated manner.

Even without a change of posture, certain patients exhibit marked variations in the direction and extent of the marginal motions in the course of a single examination. Some persons have such control over the muscles of the thorax that they can vary the type of respiration and the extent and direction of their marginal motion almost at will. It is important to keep in mind these differences in the costal excursion in health, because they are readily confused with similar inequalities due to disease.

There is a definite relation between the excursion of the costal margins and the type of respiration. In order better to understand this relation, we instructed the subjects in this group to use the different types

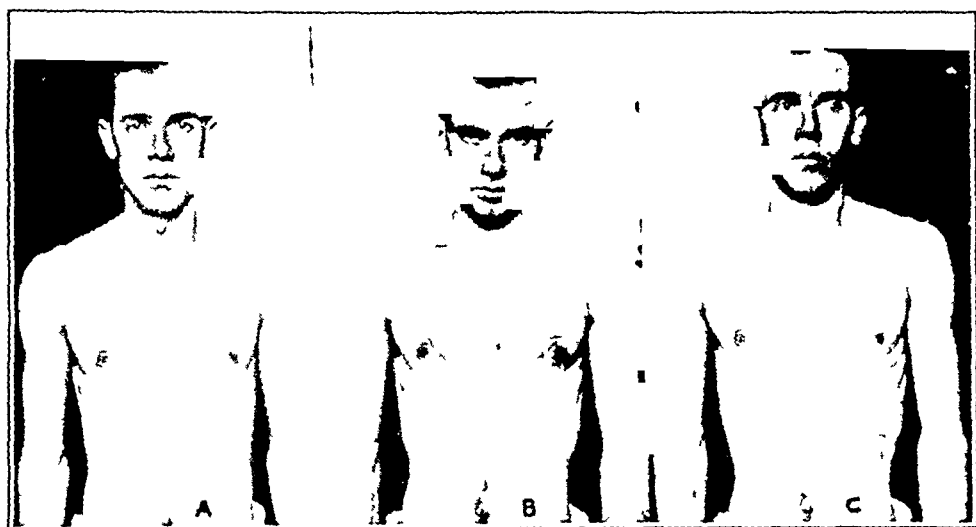


Fig 1—*A*, healthy subject, abdominal inspiration. Respiration is conducted by the piston-like excursion of the diaphragm and the costal margins are practically stationary. *B*, lower thoracic inspiration. The thorax as a whole is not elevated and the costal margins move outward. *C*, upper thoracic inspiration. The thorax is elevated as a unit and the costal margins move upward and inward.

of breathing. It was noted that on purely abdominal inspiration (fig 1, *A*) the costal margins are practically stationary. On abdomino-thoracic breathing, the outward excursion of the costal margins increases proportionately with the participation of the thoracic element, and is greatest when the respiration is purely thoracic.

The two types of thoracic respiration, lower and upper, influence the direction in which the costal margins move. On lower thoracic inspiration, the thorax as a whole is not elevated and the costal margins move outward (fig 1, *B*), on upper thoracic inspiration the thorax is elevated as a unit by the accessory respiratory muscles of the neck, shoulder girdle and upper part of the thorax, and the costal margins move upward and inward (fig 1 *C*). When the inspiration is partly upper and partly

lower thoracic, the inner portion of the costal margin may move inward, while the outer portion may move outward. In other words, with thoracic breathing, the extent of the excursion of the costal margins depends on the depth of the respiratory effort, but the direction of their movement is governed by the type of respiration. This holds true whether the person is sitting, standing or supine.

With the aid of the fluoroscope, tracings were made of the outline and position of the diaphragm on lower and on upper thoracic inspiration in the same subject at the same sitting (fig 2). When compared, the tracings showed no significant differences, demonstrating thereby that the observed variations in the direction of the costal movements were not

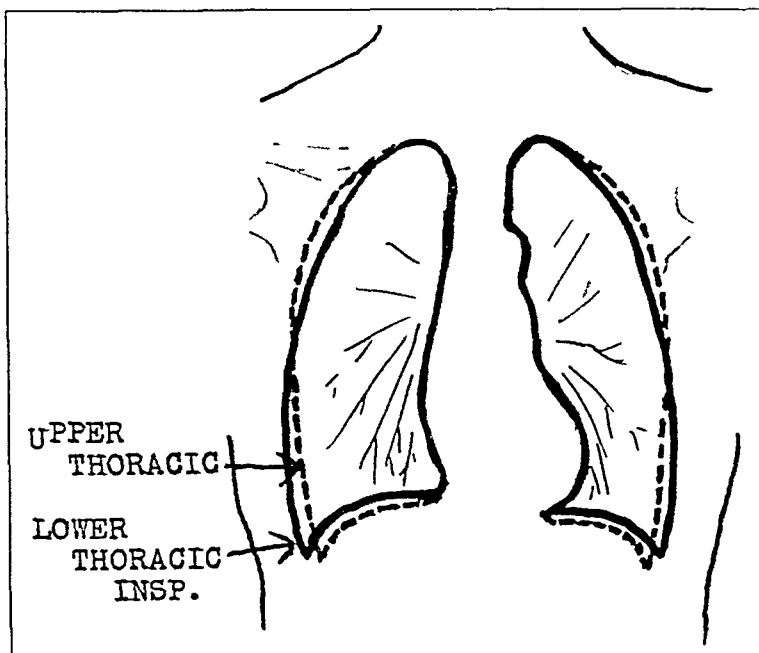


Fig 2—Composite diagram. The unbroken line represents the outline of the diaphragm on lower thoracic inspiration, the dotted line, on upper thoracic inspiration, as determined by fluoroscopic examination. The contour of the lines and their relative positions may vary somewhat in different persons but not markedly.

due to changes in the position and contour of the diaphragm. In brief, normal persons, by controlling the type of respiration, can reproduce at will the phenomena which, according to Hoover, should indicate definite pathologic conditions above or below the diaphragm.

#### EXCURSION OF THE COSTAL MARGINS IN DISEASE

With the foregoing observations in mind, we studied a group of diseases which either modify the excursion of the costal margin or effect changes in the position, contour and tonicity of the diaphragm. The

conditions studied comprised pleural effusions, pleuritic adhesions, pneumothorax, phrenicotomy, bronchial asthma, cardiac decompensation and ascites

The same method of examination was adopted as in the healthy series, provided the condition of the patient permitted. In a few instances, only a single observation was made, in the others, the observations were repeatedly checked over a period of weeks or months.

*Pleural Effusions*—The relation between the costal excursion and the depression of the diaphragm was studied in twenty-five patients with all degrees of effusion into the thorax, from small amounts to massive collections completely filling the affected side. The patients in most instances were kept under observation until the effusions had spontaneously absorbed, which permitted us to study the behavior of the costal margins with the diaphragm at widely different levels.

In twenty instances, including some of the larger effusions, no inward movement of the costal border on inspiration could be observed at any time. In the remaining five patients with massive effusions causing marked dyspnea, we detected an inward inspiratory movement of the costal border on the affected side. On inspiration, these patients flexed the thorax toward the diseased side to permit freer expansion of the healthy lung, when the dyspnea was relieved by the removal of a large amount of the fluid, the lateral flexion and the inward motion of the costal border promptly disappeared. This inward movement of the costal margin cannot reasonably be attributed to depression of the diaphragm, because, as previously noted, a similar movement of the margin occurs in healthy persons when the thorax is flexed.

It is conceded that a depression of the diaphragm by pleural effusion is often accompanied by modification of the costal excursion, but it is doubtful if the modification is caused by the alleged mastery gained by the flattened diaphragm over the antagonistic pull of the intercostal muscles. The wall of the chest is shoved outward to make room for the effusion just as the diaphragm is forced downward and the mediastinum is pushed inward. The costal border, being already held expanded by the fluid, is unable to respond in a normal manner to the outward impulse of inspiration and its movement is naturally modified.

*Flattening of the Diaphragm Due to Costophrenic Adhesions*—In twenty-four cases we observed pleuritic adhesions between the diaphragm and the ribs, obliterating the costophrenic sinus (fig 3, *A* and *B*). These localized adhesions caused various degrees of flattening of the diaphragm depending on their level. They diminished the diaphragmatic excursion, but so far as we could tell, did not interfere with its "activation." The lung above the flattened diaphragm was free from disease, or practically so in most of the cases so that any

deviation of marginal motion could be attributed solely to change of contour of the diaphragm. This flattening of the diaphragm had no influence on the costal excursion on the affected side of the chest during quiet breathing. On deep breathing no change was noted in approximately half of the cases; in the remaining cases, the flare of the affected costal margin was restrained to a greater or less extent. Yet in no instance did the costal margin move inward on inspiration except when there was a lateral sway of the thorax. In other words, the loss of convexity of the diaphragm even to the point of flattening, failed to give the diaphragm mastery over the intercostals as Hoover contended.

*Pneumothorax*.—The costal margins were studied in twenty-seven patients<sup>4</sup> in whom the affected lung had been partly or completely

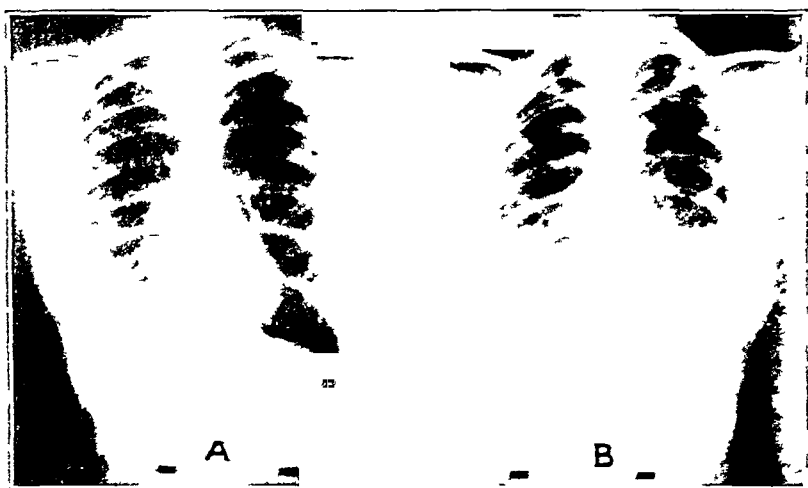


Fig 3—Comparison of the levels of the right and left diaphragmatic leaves on (A) deep and (B) quiet inspiration shows the right diaphragmatic leaf flattened and its motion greatly limited.

collapsed by artificial pneumothorax (fig 4). In some, the diaphragm as observed by the fluoroscope retained its normal convexity; others showed every variation from this normal curve to absolute flattening and complete loss of its arch. In most instances the motion of the affected side, including its costal margin, was restricted while the direction of the movement conformed to that observed in the healthy subject. In the abdominal type of breathing the costal margin did not move; in the lower costal type it moved outward; in the upper costal type of breathing it moved upward and inward. It was not observed that the presence or absence of diaphragmatic convexity influenced the direction of the marginal motion.

<sup>4</sup> Many of these patients were seen through the courtesy of the staff of the United States Veterans' Hospital, Tupper Lake, N. Y.

*Paralysis of One Leaf of the Diaphragm*—There were six patients observed in whom a phrenicotomy had been performed. On the side on which operation was performed, the diaphragm was paralyzed and assumed a position of extreme convexity in the thorax. According to Hoover, this should place the diaphragm at a great disadvantage, and the complete control of the intercostals should be reflected in a marked increase in the outward movement of the costal border on the affected side. Lemon<sup>5</sup> was unable to discover any change in the movements of the thorax in dogs after phrenic neurectomy. McKay<sup>6</sup> observed the excursion of the costal margin previous to and after phrenicotomy in twenty patients with pulmonary tuberculosis and did not note any change in its excursion following the operation. The cases observed by us like-



Fig. 4—Artificial pneumothorax. The left diaphragmatic leaf is greatly depressed and flattened, yet the left costal margin moved normally outward on inspiration.

wise did not show any change in the movement of the costal margin following operation.

*Asthma*—A series of observations was made on twelve patients suffering from periodic attacks of asthma. While they were free from spasm of the bronchi, their breathing was normal, of the lower costal type, and the excursion of the costal margin was outward. Tracings were made of the diaphragm during this time. When bronchial spasm

<sup>5</sup> Lemon, Willis S. The Physiologic Effect of Phrenic Neurectomy, *Arch Surg* **14** 345 (Jan.) 1927.

<sup>6</sup> McKay, Raymond C. Cleveland City Hospital, Cleveland, personal communication to the authors.

recurred to a degree producing urgent dyspnea, the breathing was changed to the upper costal type and the costal margins moved upward and inward. Tracings were made of the position and movements of the diaphragm during this time, and were compared with those made while lower costal breathing was being carried on (fig 5). The difference in the position or contour of the diaphragm in the two types of breathing was negligible and inconstant.

The study of the costal excursion and the position and contour of the diaphragm in asthmatic patients during and after an attack of bronchial spasm demonstrates unmistakably that the direction of marginal motion is not due to an alteration in the contour of the diaphragm,

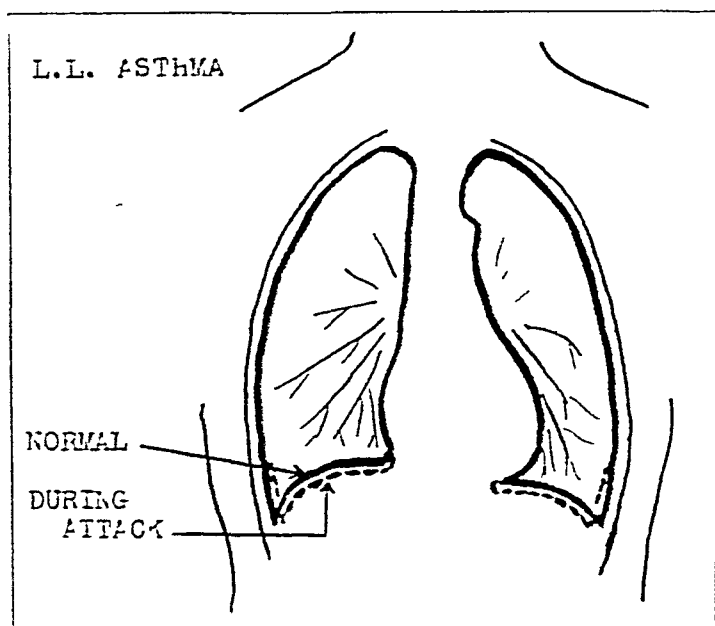


Fig 5—Asthma. The dotted line represents the position and contour of the diaphragm during an attack of bronchial spasm, the unbroken line, after the attack had subsided.

but to the change in the type of breathing necessitated by the respiratory demands.

*Nonpulmonary Conditions*—We made observations in a number of patients with dyspnea resulting from cardiac decompensation. While the patient was free from dyspnea lower costal breathing with the attendant outward movement of the costal margin was seen. When the dyspnea was urgent the breathing changed, became upper costal in type, and the costal margins moved up and in. Fluoroscopic inspection of the diaphragm during both periods did not show any demonstrable change in its contour or position.

We observed the marginal motion in a few patients with extra-thoracic disease with dyspnea, including ascites and uremia, and found

that the extent and the direction of the costal movement is determined by the type of respiration at the moment of observation

#### CONCLUSIONS

In our experience, the extent and direction of the excursion of the costal margin bear little if any relation to the position or contour of the diaphragm. The extent of the excursion of the costal margins depends on the depth of the respiratory effort, but the direction of their movement is governed by the type of respiration. Their movements may vary from time to time in the same patient, whether the disease is thoracic or extrathoracic, and can be reproduced at will by healthy subjects. We are forced to conclude that the modifications of the marginal motions which have come to be called "Hoover's sign" are not reliable guides to underlying pathologic conditions.



# OCHRONOSIS

## REPORT OF A CASE OF CARBOLOCHRONOSIS<sup>†</sup>

S E GOLDBERG, M D

DETROIT

Up to the present time there have been few reports in the English literature on the subject of ochronosis. The term ochronosis (Greek, pale yellow) was applied by Virchow,<sup>1</sup> in 1866, to the pigmentation of cartilages and cartilage-like tissues found at autopsy in a man, aged 67, who died of an aneurysm of the ascending aorta. Fine microscopic sections showed the pigment to be yellowish (ochre colored), but grossly the pigmentation was blackish. Indeed, the "rib cartilages, pelvic synchondrosis, and the intervertebral disks were so black that they appeared as if they had been dipped into ordinary ink." Since Virchow's time, fifty-one cases have been reported.

Albrecht<sup>2</sup> (1902) first suggested the relationship of ochronosis to alkaptonuria. Osler<sup>3</sup> (1904), however, was the first to recognize the condition clinically; he reported two cases of ochronosis with alkaptonuria which occurred in brothers. The clinical diagnosis was made because of the deep pigmentation of the cartilages of the ears and of the sclerotics in both and, in addition, in one of the brothers, of a remarkable ebony black discoloration of the skin of the nose and the cheeks.

In 1906, Pick<sup>4</sup> in Germany and Pope<sup>5</sup> in England each described a case of ochronosis which in each instance occurred in a patient who had applied wet dressings containing small amounts of carbolic acid to chronic ulcers of the leg continually over a period of many years. The pathogenesis of this disease was not discussed by Pope but was first pointed out by Pick, who recognized an exogenous form of ochronosis due to the introduction of phenol into the body, and an endogenous form occurring in patients with alkaptonuria. Pick also showed the pigment

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<sup>†</sup> Submitted for publication, Sept 27, 1928.

<sup>\*</sup> From the Department of Pathology of the Krankenhaus-im-Friedrichshain, Berlin. Prof Ludwig Pick, Director.

1 Virchow, R. Ein Fall von allgemeiner Ochronose der Knorpel und knorpelähnlichen Teile. Virchow's Arch f path Anat **37** 212, 1866.

2 Albrecht, H. Ueber Ochronose, Ztschr f Heilk **23** 366, 1902, Zdzarek, E. Ueber den chemischen Befund bei Ochronose der Knorpel, *ibid* **23** 379, 1902.

3 Osler W. Ochronosis. The Pigmentation of Cartilages, Sclerotics, and Skin in Alkaptonuria, Lancet **1** 10, 1904.

4 Pick L. Ueber die Ochronose, Berl klin Wchnschr, April and May, 1906, vols 16 to 19 incl.

5 Pope, F M. A Case of Ochronosis, Lancet **1** 24, 1906.

to be closely related to melanin, although it differed from melanin in its chemical properties in a few minor details. In alkaptonuric ochronosis, the pigment results from the hydroxylated substances of the aromatic series (tyrosine and phenylalanine) under the influence of oxydative ferments (tyrosinase), in carbolochronosis, the pigment results from the hydroxylated benzol derivatives, hydrochinon and pyrocatechin. In alkaptonuria, there is a checking of the normal protein metabolism at an intermediate stage. Unlike the normal person, the alkaptonuric patient cannot burn the homogentisic acid (alkapton body) formed out of tyrosine and phenylalanine and therefore partly secretes it as such in the urine and partly stores it in certain of the body tissues in which it gives rise to the ochronotic pigment. In exogenous ochronosis, the pigment is the same, though it arises from hydrochinon.

In addition to the occurrence of the ochronotic pigment primarily in the cartilages and the cartilaginous tissues, Pick showed that the pigment might be deposited diffusely in the loose connective tissues, e.g., in the adventitia of the blood vessels, in the corium of the skin and in the smooth and striated muscles, as well as in the epithelial parenchyma of the kidney. He also raised the question of a third form of ochronosis, that associated with melanuria. Oppenheimer and Kline<sup>6</sup> reported a case which they believed falls into this category. This group is not sharply set off and probably includes a number of instances of alkaptonuric ochronosis.

The total of fifty-one cases may then be divided into three groups: the endogenous form which is congenital, the exogenous form due to the introduction of phenol into the body and the melanotic form of unknown origin. In every case of carbolochronosis recognized up to the present time, there has been a history of long continued application of phenol as an antiseptic dressing to ulcers on the leg. Since phenol is used in various ways in industry, it would be theoretically possible also to have carbolochronosis result from industrial poisoning, although good protective methods could probably guard against such an occurrence. As the era of the popular use of carbolic acid as an antiseptic is past, carbolochronosis may be said to be a dying disease. I am therefore reporting another case in which autopsy was performed and which has been studied especially from the point of view of the cartilaginous changes. Ella H. Fishberg,<sup>7</sup> who carefully treated the subject of carbolochronosis in 1924, collected reports of eleven cases in the world's literature. The following case will be the twelfth. In eight of these twelve cases, postmortem examinations were made, in four of the eight by Professor Pick.

6 Oppenheimer, B. S., and Kline, B. S. Ochronosis, *Arch. Int. Med.* **29**: 732 (June) 1922.

7 Fishberg, Ella H. Ueber die Carbolochronose, *Virchows Arch. f. path. Anat.* **251**: 376, 1924.

## REPORT OF CASE

*History*—M. M., a woman, aged 63, unmarried, formerly a cook, was admitted to the Hufeland Hospital (Dr. Winter, director) on Aug. 28, 1925. The parents had died at an advanced age. Of the seven brothers and sisters, four sisters were still alive. In the fourth decade of life, the patient suffered for six years with rheumatism of the joints. She had one child. As a result of frequent prolonged standing while she was working as a cook, varices developed on both legs, and since the age of 32, she had had ulcers on the right leg, since her thirty-ninth year, ulcers had been present on the left leg also. For eleven years she was treated for the ulcers with zinc paste bandages, but the ulcers always broke down. Then for a number of years the patient treated the ulcers with applications of phenol solution, for just how long she could not state. Finally, because of continual confinement in bed, she was admitted to the hospital.

*Physical Examination*—The patient had a small and delicate frame, which showed fair development and nutrition. The skin and mucosae were generally pale. Edema or exanthems were not present. On both ears over the cartilages, there was a striking bluish-gray coloration, which shimmered through when looked at from the inner surface. On each eye, there were two bluish-black spots beside the corneas. The organs of the neck and throat showed nothing of importance. The cardiac borders were not widened. A systolic murmur was heard all over the precordium, most prominently over the apex. The pulse rate was from 84 to 88, and the rhythm was regular except for an occasional extrasystole. Percussion of the lungs was everywhere resonant, but a few medium coarse moist râles were heard over the bases. The abdomen was soft and flabby and was not tender to palpation. The liver and spleen were not enlarged or tender to palpation. Examination of the urine gave negative results. The upper extremities showed nothing of importance. On both legs, extending from about one and one-half hand breadths below the patella down to the ankles, were ulcers which embraced the circumference of the extremities but which showed fair granulation. The neurologic examination gave negative results.

*Course*—Two years later the patient was ill for several weeks, having a slight fever and paratyphoid B bacilli in the stool. Examination of the portio uteri at this time showed a crater-like carcinomatous ulcer, and the uterus was immovable. The patient was discharged on June 30, 1927.

She reentered the hospital a short time later in a marasmic state, and died on Sept. 10, 1927, aged 65.

*Autopsy* (Professor Pick)—Autopsy was performed on Sept. 10, 1927. The body was that of a small woman of weak bodily frame. General anasarca was present, the edema being quite marked in the arms and legs. The auricles of the ears showed a striking bluish-gray coloration, which was especially prominent in the conchae. Near the cornea of each eye were two bluish-black spots, resembling parentheses. The skin of the face and elsewhere and the visible mucous membranes showed pallor but no pigmentations. On both legs, extending from the middle downward to the ankles and embracing the entire circumference, were ulcers having irregular outlines with firm, stiff borders and smooth reddened bases. When the outer soft tissue of the thorax was removed, the entire cartilaginous tissue of the thorax was seen to appear bluish and to shimmer, thus appearing in sharp contrast to the reddish ossified ribs. Ascites were not present. The right diaphragmatic leaf reached to the level of the fourth rib, the left to the level of the fifth rib. In the small pelvis, a hard mass surrounded the firmly walled-in uterus. Both lungs were fixed by numerous flat adhesions. Effusion was not

found in the pleural or pericardial sacs. The heart was of normal size, the chambers were not dilated, the mitral and aortic valves were firm and fibrous and showed light atherosclerotic spots. The musculature was firm and without special significance. The sinuses of Valsalva were markedly widened. At the beginning of the aorta ascendens were calcified plaque-like deposits. The coronary arteries were firm and wide and showed yellowish internal surfaces. Nowhere on the valves, chordae tendinae, or on the intima of the ascending aorta were there pigmentations. The left lung was large and heavy, in places having a lessened air content. On section it was rich in blood and foamy. In the lower lobe posteriorly in a localized area, there was no air, a cloudy fluid exuded on pressure. The bronchial mucosa was reddened. In the main bronchus and its larger branches, there was no evident staining of the cartilage rings. The general condition of the right lung was the same as that of the left. Here, also, in the lower lobe and anteriorly in the upper and middle lobes were atelectatic areas, which on pressure exuded a cloudy fluid. The cartilages of the main bronchus and its branches resembled that of the left, and these were also free from pigmentation. The pharynx, palates, palatine tonsils, tongue, larynx and esophagus were normal. The thyroid was large, and the middle lobe was well developed. The thyroid cartilage showed a striking grayish-blue coloration, as did also the cartilage rings of the trachea.

The spleen was of the usual size and was flabby and slightly firm. On section, it was brownish red, moist and smooth, and the trabeculae were evident. The suprarenals did not show anything of importance. The pelvic organs were removed with the ureters and kidneys. The urinary bladder showed a slight mucosal injection at the base. The mouth of the ureters was patent. In the trigone, the lymph follicles were evident. The middle and the upper third of the vagina, the cervix and the corpus uteri up to the fundus were fully replaced by opaque, grayish-yellow, putrid, disintegrating masses of tumor tissue. In the remaining preserved yellowish portion of the fundus, the muscle wall was 1 cm thick and contained firm blood vessels. The mucosa showed fresh hemorrhage. Wide flat adhesions covered the fundus uteri, the space of Douglas and the appendages. Both tubes were closed, club-shaped, distended with fluid and flabby and were about the thickness of the small finger. The right ovary was about as large as an almond and densely firm. The left was even smaller. The rectal mucosa was slightly edematous but otherwise free. The left ureter was not especially widened, and its mucosa was pale. The left kidney measured 12.5 by 6 by 3 cm and was flabby in appearance. The kidney pelvis was extraordinarily widened, having a number of small concretions ranging in size up to that of lentils and having a pale mucosa. The parenchyma was yellowish, and the markings were poorly seen. The right ureter was as thick as a finger, its mucosa was like that of the left. The right kidney measured 10.5 by 5 by 2.5 cm. Here the pelvis was also greatly dilated and had a pale mucosa. The cortex was narrow and had poor markings. The stomach showed old scars in the middle of the small curvature, its mucosa was otherwise free. The extent of the ligamentum hepatoduodenale was free. The liver measured 25 by 17 by 5 cm and was flabby but somewhat firm, the lobules were large and had sunken centers which were reddish while their peripheries were yellowish. The pancreas and the intestines were free.

The aortic and thoracic aorta showed numerous sclerotic spots and calcified plaques. The plaques in the arch were surrounded by areas of grayish coloration, the abdominal aorta was like the thoracic aorta but without visible areas of pigmentation.

The pia mater and its blood vessels at the base of the brain were delicate. The brain was pale and slightly moist. In the right lenticular nucleus was an elongated area of softening about twice the size of a hemp seed. The vertebral column was removed and after being sawn through the middle, did not show striking pigmentation.

*Anatomic Diagnosis*—The condition was diagnosed as disintegrating carcinoma of the vagina, cervix and fundus uteri and bilateral hydrosalpinx. Old adhesions of the uterus and its adnexae, widening of the ureters and bilateral hydronephrotic kidneys, fibrosis and atherosclerosis of the mitral and aortic valves, widening of the sinuses of Valsalva, numerous old pleural adhesions, hyperemia and edema of the lungs, hyperemia of the bronchial mucosa, bronchopneumonia of the left lower lobe and of all the lobes of the right lung, atherosclerosis and calcification of the aorta, a small area of softening in the right lenticular nucleus, old scars of the mucosa of the stomach, slight edema of the rectal mucosa, general anasarca and large circular callous ulcers of both legs were found.

Ochronosis of the cartilage of the ears and ribs, the thyroid cartilage, cartilage rings of the trachea and the main bronchi and ochronotic spots in both sclerae and about the calcified deposits in the intima of the aortic arch were also found.

The bony and cartilaginous tissues that were removed were then studied more minutely.

(1) *Sternum, Cartilaginous and Bony Parts* The generally bluish shade of the cartilage of the ribs became changed to a dark gray after removal of the perichondrium. On this dark gray background, there appeared a great number of small dark brown spots which increased in size up to that of a lentil and which in many instances also became confluent. Under the surface and toward the depth the cartilage was pigmented in all directions and was diffusely grayish brown to brown.

(2) *Larynx and Respiratory Passage* (fig 1) The thyroid cartilages, covered with perichondrium, showed a blue shimmer. On section (see left thyroid cartilage in figure 1) they were brown. The cartilage rings of the trachea, freed of perichondrium, showed a play of various colors. In part they were brownish yellow to yellow, in part light to dark brown with irregular arrangement of this shade. On cross-section also, the dark brown predominated.

(3) *Joints* (a) *Shoulder joints* The heads of both humeri were smoky gray and showed a somewhat darker shade only toward the border of the surface of the joint. In about the middle of the head of each joint there was a smaller collection of irregular spots. The cartilage itself was smooth. The surface of the joints on both shoulder blades was grayish brown, in the center there was speckling of dark brown spots about twice the size of a lentil, while toward the border of the under surface of the joint there was grayish-brown pigmentation. The brownish color was well seen on cross-section at the point of attachment of the tendons. The cartilage and the intercartilaginous substance of the sternoclavicular joint were light brown. The cartilage elsewhere was without change. (b) *Hip joints* The cartilage of the heads of the femurs was dark grayish-brown, especially about the attachment of the ligamentum teres, where the spotting was darker bluish and in places grayish black, particularly about the cartilage border. In general the cartilages were smooth, but here and there they had a slight superficial rawness, especially about the point of attachment of the right ligamentum teres, but not about that of the left side. (c) *Knee joints* Both knee joints showed a diffuse brownish shade of the cartilage and dark gray spotting on the menisci and the cruciate ligaments. The latter were spotted brownish on cross-section. On the



Fig 1—Fresh specimen showing ochronotic pigmentation of the thyroid, tracheal and bronchial cartilages



Fig 2—Head of left femur showing distribution of the pigment



cartilage of the knee joint a darker spotting on the brownish substratum was present in places. The cartilage everywhere was smooth.

For the microscopic examination of the cartilage, only those specimens could be used in which frozen sections could be made without previous decalcification in nitric acid, since the nitric acid lends a diffuse yellowish tone to the tissue. In this way the examinations were carried out on flat little disks removed from the heads of the femurs and on little pieces of cartilage from the ear. The intactness of the cartilage and also of the ground substance was seen microscopically. The ground substance was pigmented with lighter intensity, varying in color from yellowish to brownish. Granular pigmentation was not found.

Treatment of the sections with 2 per cent silver nitrate solution for three days caused a darker browning, treatment for four days with 3 per cent hydrogen peroxide solution removed the color from the sections completely. One of the darker spots of the sclera was also investigated, and here also the staining of the bundles in the sclera was diffusely light brownish yellow, without deposition of the granular pigment.

The new growth in the uterus was shown to be a simple carcinoma.

The chemical examination (Dr. Brahn) was so carried out that the broken up pieces of stained cartilage from the rib were first treated with 5 per cent cold sodium hydroxide solution to extract the pigment. The staining material did not go into solution. The sodium hydroxide solution was then strengthened to 10 per cent and the mixture warmed for a considerable time on the water bath, centrifugalized, and after dilution with water, filtered. The filtrate was precipitated with concentrated sulphuric acid, giving a faint yellowish-brown deposit.

#### CLINICAL FEATURES

Alkaptonuria is an endogenous disease occurring in families in which there has been inbreeding, particularly when the parents are cousins (Umber and Bueger<sup>8</sup>). Alkaptonuric ochronosis occurs most frequently in persons in the fifties, although cases have been reported in patients of 23, 30 and 31 years of age.

The clinical diagnosis is made on the presence of pigmentation of the skin, urinary manifestations and the history. In alkaptonuric ochronosis, the examination of the urine confirms the diagnosis. In carbolochnosis, there is a history of long-continued use of carbolic acid washes or dressings. In ochronosis of both groups the external pigmentation may be found in the skin of the face, axillae, hands, the sclerae, the mucosa of the lips and the cartilages of the nose, eyelids and ears. The sweat and cerumen may be stained brownish to blackish. The pigmentation of the face is usually described as yellowish brown and that of the auricles light gray brown to dark blue. Each cornea may be embraced on either side by a group of thickly set, bluish-black, sharply demarcated spots, in form suggesting parentheses. The cartilages may be stained yellowish brown to grayish blue, and even as black as coal, ebony wood or ink. In carbolochnosis, the cartilages are apt to be less intensely

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8 Umber and Bueger, M. Alkaptonurie mit Ochronose und Osteo-Arthritis deformans, *Zystinurie*, *Deutsche med. Wchnschr.* **39** 2337, 1913.



stained In general the pigment of carbolochronosis is less intense than that of the endogenous form, as is to be expected, since the endogenous form exists through the whole lifetime, whereas the exogenous form is the result of an action occurring a number of years and usually beginning in midlife

The urine may be dark when it is voided or may become dark after a varying period of exposure to the air Copper solutions are sometimes reduced In alkaptonuria the alkapton body may be detected, while phenol and phenol derivatives have been found in the urine in some cases of carbolochronosis Pick stated that in cases of ochronosis in which the condition is more or less limited to the internal tissues, the finding of ochronotic casts in the urine should establish the diagnosis

In addition, changes in the joints and the constant finding of cardiovascular lesions have been associated with ochronosis In alkaptonuric ochronosis, destructive changes in the larger joints and spine are frequently present, particularly arthritis deformans, while in carbolochronosis, changes in the joints have been described but are less constant and seldom severe In the former type of ochronosis, the condition usually begins to develop in the joints of patients in the forties, while in the latter type, most patients first begin the use of phenol applications in the forties This may be the reason for the lesser frequency of arthritic changes in carbolochronosis Kolaczek<sup>9</sup> reported the occurrence of ochronotic nodes on the tendons of the foot

The constant association of arteriosclerosis with the frequent occurrence of endocarditis has been mentioned by most writers and would seem to be more than a mere chance relationship

The cessation of the introduction of phenol into the body may lessen the intensity of the external pigmentation (Poulsen,<sup>10</sup> Fishberg), lighten the color of the urine and effect an improvement in the "carbol marasmus" On the other hand, Gross and Allard regarded the alkaptonuric ochronosis as "an advancing incurable suffering which, if sufficiently intense and of long enough duration, leads to a marked injury in health"

Examination of the blood may reveal the presence of homogentisic acid, tyrosine, tyrosinase or phenylalanine

#### PATHOLOGIC FEATURES

Besides the pigmentation of the skin and the cartilages, the pigment may also be found in the connective tissues (intervertebral disks, synchondrosal menisci, ligaments and tendons), in the intima of the

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9 Kolaczek, H Ueber Ochronose, Beitr z klin Chir 71 254, 1910

10 Poulsen, V Ueber Ochronose bei Menschen und Tieren, Beitr z path Anat u z allg Path 48 437, 1910

aorta, in smooth, striated as well as in cardiac muscle and in the epithelial cells, either as a diffuse or as a granular deposit

*Skin*—A brownish yellow pigment is deposited in the stratum germinativum of the skin epithelium

*Sclera*—There is a difference of opinion among various authors as to whether the pigment is collected in the ocular connective tissue or in the sclera. My observations have shown that the pigment is in the sclera.

*Cartilages*—The thyroid, cricoid, tracheal and bronchial cartilages as well as those of the ears, nose, eyelids, ribs and joints are affected. In unstained microscopic sections of cartilage from the ribs, the pigment is yellowish, diffuse or granular and is most intensely deposited immediately beneath the perichondrium and little in the central cartilage. Because the most concentrated deposits of pigment take place at the locations in which the cartilage is most closely bordered by the blood vessels or immediately beneath the perichondrium, Pick has formulated his "basic law for ochronosis pigmentation" in explanation of this distribution.

*Connective Tissues*—The patellar ligament may show smoky gray to brownish gray pigmentation, while the intervertebral disks and ligaments, as well as other tendons and connective tissues, may also show the deposition of pigment.

*Vascular System*—Changes in the vascular system have been present in all the reported cases that have come to autopsy. Besides the presence of arteriosclerosis, which may be ascribed in part to the age of the patients, endocarditis was present in a number of cases. In one instance Pick found blackish pigmentation on the valves of the heart, diffuse brownish gray and grayish black pigmentation in the intima of the aorta and iliac arteries, blackish collections of pigment about the calcium plaques and blackish streaks in the smooth places. Kolaczek spoke of the condition of the heart and blood vessels as an index to the severity of the ochronosis, and since Viechow's time it has been repeatedly confirmed that the ochronotic pigment binds itself on to the arteriosclerotic lesions in the heart and blood vessels.

*Kidneys*—Pick described various changes in the kidneys: diffuse yellowish brown shades of the epithelial parenchyma, tiny cysts which correspond mainly to segments of urinary canaliculi with blackish or colorless content, ochronotic infarcts of the pyramids, coal-black, hard ochronotic concretions in the pelvis, and ochronotic casts filling the tubuli recti, appearing hyaline or granular and staining light bluish with hemalum. Allard and Gross<sup>11</sup> also described black ochronotic concretions in the kidney pelvis.

11 Allard, E., and Gross, O. Untersuchungen ueber Alkaptonurie, Ztschr. f. klin. Med. 64 359, 1907

*Joints*—The arthritic changes are varied and chronic, being variously designated as chronic arthritis, arthritis ulcerosa sicca, arthritis adhaesiva ankylopoetica and arthritis deformans. Benecke called attention to "the typical dry destruction of the degenerating joint cartilages." He characterized the splintering up of cartilage into little spearlike pieces as peculiar to chronic arthritis of alkaptonuric ochronosis, stating that it does not occur in other forms of arthritis. Arthritic changes, however, have been reported in carbalo ochronosis also, but thus far these changes have not been of an extreme type. The changes in the joints in ochronosis have been likened to those of gout, homogentisic acid being deposited in the joints in the one case and uric acid in the other.

Kolaczek showed that the places in the cartilages that stained most intensely were likewise the most severely damaged. Landois,<sup>12</sup> Allard and Gross and Kolaczek regarded the deposition of the staining material in the cartilages as the etiologic factor for the arthritis. Fishberg called attention to the fact that the arthritis does not depend on the ochronosis but rather on the homogentisic acid or the hydroxylated phenol derivative.

The arthritic and atherosclerotic changes and those in the tendons may therefore all be connected to the homogentisic acid circulating in the blood. According to Pick, the ochronotic pigment has especial attraction for cartilage in the stage of regressive metamorphosis as it generally has for other regressively changed tissue and for vitally weakened cells or for degenerating intercellular substance. The accumulating pigment then increases the injury to the tissue, thus setting up a vicious circle.

#### MICROCHEMICAL REACTIONS

Pick first accentuated the relationship of the pigment to melanin and showed the two pigments to differ only in a few minor details. The ochronotic pigment is soluble in alkali and insoluble in chloroform, predominantly, it has the characteristics of an acid but is amphoteric to a degree, since it is also slightly soluble in hydrochloric acid. Like melanin, microscopically it does not contain iron, like certain melanins, it does not contain sulphur. Microscopic sections stained with sudan and osmic acid give negative reactions. The pigment bleaches after prolonged soaking in hydrogen peroxide and blackens with certain silver methods especially well with the method of Bielschowsky.

#### PHYSIOLOGIC FEATURES

Katsch<sup>13</sup> showed that a series of colors could be produced by various degrees of oxidation of homogentisic acid (by hydrogen peroxide)—

<sup>12</sup> Landois, F. Zur Kenntniss der Ochronose, Virchows Arch f path Anat 193 275, 1908

<sup>13</sup> Katsch, G. Ist ein Ferment defekt Ursache der alkaptonurischen Stoffwechselstörung? Klin Wchnschr 5 1994, 1926

straw yellow, pink, red, brown and black. Phenylalanine and tyrosine (von Fürth <sup>14</sup>) have special capacity as color builders. Katsch expressed the belief that various colors can be similarly produced by the action of tyrosinase on tyrosine and homogentisic acid in the body. On this basis, Pick gave his explanation of the genesis and peculiar distribution of the ochronosis. In the genesis of the carbolochronosis, hydrochinon and pyrocatechin are substituted for tyrosine and homogentisic acid in the alkaptonuric ochronosis. The special affinity of the degenerating, and especially of the sclerotic, tissues for the ochronosis pigment may be explained as due to the limited metabolism and sparse oxidation in these places.

#### SUMMARY

A case of endogenous ochronosis due to long continued application of wet phenol dressings to chronic ulcers of the leg is reported. Special reference is made to the pathologic changes in the bones and cartilages. The various clinical and laboratory features of the different types of ochronosis are enumerated and briefly discussed.

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14 Von Fürth, O. Physiologische und chemische Untersuchungen ueber melanotische Pigmente, *Centralbl f path Anat u z allg Path* **15** 617, 1904

# OPIUM ADDICTION

## I THE CONDUCT OF THE ADDICT IN RELATION TO INVESTIGATIVE STUDY \*

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The data to be presented in a series of papers, of which this is the first, have been obtained from studies of persons addicted to opium or its derivatives who have applied for treatment at the Narcotic Wards of the Philadelphia General Hospital. These wards are maintained by the city of Philadelphia and have no relationship to law enforcement agencies. In this introductory paper, we wish to present our impressions of the behavior of the addict for the purpose of emphasizing the existence of obstacles which, if not fully appreciated, may result in failure of investigative efforts. A detailed report of the psychiatric and psychologic studies will be published later by members of the staff investigating this phase of the problem of opium addiction.

### REASONS FOR SEEKING TREATMENT

The person who presents himself for treatment in these wards does so of his own volition and for one or more of the following reasons. He is disgusted with his slavery to the drug, he desires temporary refuge from the police, or for financial reasons he wishes to reduce the amount of his daily dosage or to obtain free maintenance for a time. Regardless of the motive for seeking treatment, patients who apply for admission either have had an unusually large dosage (as they express it, are well "shot-up") or are manifesting early withdrawal symptoms. In either event, they will agree to any sort of experimentation as long as it promises their immediate or early acceptance for treatment. This apparent desire on their part to cooperate must not be taken seriously, as we will point out later.

### RELATIONSHIP TO DRUGS

After a person has become firmly addicted to the use of opium or one of its derivatives, we have reason to believe that the problem of

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\* From the Narcotic Wards of the Philadelphia General Hospital

\* Expenses of this research were defrayed by the Committee on Drug Addictions, New York City. The research was carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction, in the wards of the Philadelphia General Hospital which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia.

securing and maintaining an adequate supply of the drug comes to be the major purpose of his existence. To an extraordinary degree, he develops a sagacity and persistence in this direction which may outmatch the abilities of those who are conducting the investigation. The ingenuity that is displayed in maintaining channels of supply is amazing. We have come to believe that practically every word which the addict utters and every deed which he may perform are based directly or indirectly on a motive concerned with the maintenance of these channels of supply. He will plead with or threaten those about him who are in a position to supply him with the drug. Whatever method he may use has been previously determined by careful consideration on his part as to which may be the more successful.

Undoubtedly there are some who desire to give up the drug on account of disgust and give this reason in all sincerity. The patients encountered in the wards of the Philadelphia General Hospital are practically all from the so-called underworld. A considerable number of them have, however, at one time lived in better circumstances. Not any of them has fallen so low as to fail to realize that he is an outlaw under present conditions of the law and public opinion. This realization together with the undoubted tax on their mental processes levied by the very ingenuity which these persons display is enough to bring about this so-called disgust with the drug. This feeling, however, quickly vanishes when the addict is confronted with the sufferings attendant on failure of supply of his drug.

#### GENERAL BEHAVIOR IN THE WARD

After admission to the ward with the knowledge that the drug is available and will be supplied for certain lengths of time, the addict becomes amenable. His behavior is excellent, and he desires to cooperate in any experiment which does not interfere with his daily dosage. This cooperative attitude on the part of the addict is real and sincere but lasts only as long as the effects of the drug persist, usually a matter of hours. When the effects of the drug pass off, all the sagacity and ingenuity on his part are brought into play as only those who have been associated with this type of person can appreciate.

Not only must the observer foil the schemes which the addict is devising to obtain the drug, but he must defeat plans, made before admission, for the restoration of his supply should his craving become unbearable. He may have attempted to bring the drug into the ward concealed in his clothing, letters, jewelry or in any orifice of the body large enough to hold it. Extreme care must be taken to search the addict before admission. We have found drugs concealed in the soiled dressings covering abscesses resulting from infections caused by hypodermic injections.

Should his attempts to bring a certain quantity of the drug into the ward have failed, he resorts to plans devised to obtain it from friends outside of the hospital, or he schemes with fellow addicts who are about to be discharged and who have signified their intentions to him of immediately returning to the use of the drug. He will attempt to bribe any one who appears open to temptation. Letters will come addressed to him which have been written on paper previously saturated with the drug, dried, ironed out and then inscribed with a harmless message. He will extract the drug by either chewing the paper or redissolving it in water. Sometimes the drug is concealed under the stamp of the envelop. The wooden stem of a match changed into a cylinder has been found to contain a drug. He will accuse or betray his best friend in order that he may gain favor from those in charge. Telegrams and telephone messages will arrive bringing the news of the death of a member of the family, asking his immediate return home. These are but a few of the methods employed to obtain drugs, and unless forestalled they will ruin any studies made during the withdrawal period. In addition, there is always danger that the patient may be aided by a fellow addict who may have drugs in his possession, or by a drug pedler who will furnish drugs without charge when it insures him the return of the addict with funds in the near future.

Practically 80 per cent of the addicts appearing for treatment were using heroin before admission to the wards. The rest were addicted to morphine, except one or two who used camphorated tincture of opium and tincture of opium. In the cases of morphine and heroin addiction, the hypodermic method of administration was the choice, except in several cases of sniffing and in two in which self-intravenous administration was employed. After admission to the ward, all persons used for study were supplied with drugs in the form of morphine administered hypodermically. Enough of the drug was given to allay any possible suffering. We find that morphine easily displaces heroin in maintaining comfort and rest. All studies to be reported must be considered as studies made during morphine addiction and morphine withdrawal.

While the person is under the influence of the narcotic, his behavior is normal. Not having much to do, he spends his time smoking cigarettes and engaging in conversations, chiefly on drug addiction. As a rule, the addict is interested in sporting events and the latest newspaper scandals. Although supplied with fiction of the lighter variety, he is not a consistent reader while in the ward. He eats well, sleeps well and helps to keep the ward clean, lending a helping hand to any kind of work requested. He is docile, well behaved and is altogether easy to deal with while receiving the drug and while desiring to remain in the ward.

## WITHDRAWAL SYMPTOMS

The withdrawal of the drug results in a striking change in the appearance and behavior of such a person. The symptoms which make their appearance have frequently been described in the literature (Johnson,<sup>1</sup> Levinstein,<sup>2</sup> Sollier,<sup>3</sup> Morat,<sup>4</sup> Bishop<sup>5</sup> and Lambert<sup>6</sup>). Having studied their onset carefully, we shall describe them briefly in the order of their appearance as we have observed them.

As the time approaches for what would have been the addict's next administration of the drug, one notices that he glances frequently in the direction of the clock and manifests a certain degree of restlessness. If the administration is omitted, he begins to move about in a rather aimless way, failing to remain in one position long. He is either in bed, sitting in a chair, standing up or walking about, constantly changing from one to another. With this restlessness, yawning soon appears, which becomes more and more violent. At the end of a period of about eight hours, restlessness becomes marked. He will throw himself onto a bed, curl up and wrap the blankets tightly around his shoulders, sometimes burying his head in the pillows. For a few minutes he will toss from side to side and then suddenly jump out of the bed and start to walk back and forth, head bowed, shoulders stooping. This lasts only a few minutes. He may then lie on the floor close to the radiator, trying to keep warm. Even here he is not contented, and he either resumes his pacing about or again throws himself onto the bed, wrapping himself under heavy blankets. At the same time he complains bitterly of suffering with cold and then hot flashes, but mostly chills.

He breathes like a person who is cold, in short, jerky, powerful respirations. His skin shows the characteristic pilomotor activity well known to these persons by the name of "cold turkey." The similarity of the appearance of the skin at this stage to that of a plucked turkey is striking. Coincident with this feeling of chilliness, he complains of being unable to breathe through his nose. Nasal secretion is excessive. He has a most abject appearance, but is fairly docile in his behavior. This is a picture of his appearance during the first eight hours.

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1 Communication from G. H. Smith, Esq., to Dr. Johnson, *Lancet* **1** 707, 1841-1842.

2 Levinstein, E. *Die Morphiumsucht*, 1878, p. 14.

3 Sollier, P. *La demorphinisation et le traitement rationel de la morphinomanie*, *Semaine med.*, 1894, p. 146.

4 Morat, D. *Le sang et les secretions au cours de la morphinomanie et de la desintoxication*, *These de Paris*, 1911.

5 Bishop, E. S. *Narcotic Addiction • A Systemic Disease Condition*, *J. A. M. A.* **60** 431 (Feb. 8) 1913.

6 Lambert, A. *Nelson's Looseleaf Medicine* 1920, vol. 2, p. 607A.



Often at the end of this period, the addict may become extremely drowsy and unable to keep his eyes open. If he falls asleep, which is often the case, he falls into a deep slumber well known as the "yen" sleep. It takes unusual noises to awaken him. The sleep may last for as long as eight or twelve hours. On awakening, he is more restless than ever. Lacrimation, yawning, sneezing and chilliness are extreme. A feeling of suffocation in the back of the throat is frequently mentioned. Usually at this stage, the addict complains of cramps, locating them most frequently in the abdomen, but often in the back and lower extremities. A right rectus rigidity with pain localized over the appendical region is not uncommon, one can easily be misled in the diagnosis, since at this stage a leukocytosis is frequently present, as will be pointed out in a later paper. Vomiting and diarrhea appear. He may vomit large quantities of bile-stained fluid. Perspiration is excessive. The underwear and pajamas may become saturated with sweat. Muscular twitchings are commonly present, they may occur anywhere, but are most violent in the lower extremities. He may sit in bed with his leg flexed, grasping it tightly below the knee, fearing the twitch which will suddenly throw it into complete extension and which he cannot control. If he is handed a cigaret to smoke, his hand trembles so violently that he may have difficulty in placing it in his mouth. The tremor is so marked that he is unable to light it himself.

He refuses all food and water, and frequently sleep is unknown from this point. It is at this stage that he may one minute beg for a "shot" and in the next minute threaten physical violence. Nothing can make him smile. He will beat his head against the wall or throw himself violently on the floor. Any behavior which he thinks may bring about the administration of the drug will be resorted to. Occasionally he may complain of diplopia. Seminal emissions in the male and orgasms in the female frequently occur.

We believe that the height of these withdrawal symptoms is reached somewhere between the period of forty-eight and seventy-two hours following the last dose of the drug taken. The readministration of the drug promptly brings about a dramatic change. The patient becomes exceedingly docile almost simultaneously with the puncture of the hypodermic needle. In a few minutes he begins to feel warm, and the gooseflesh and perspiration are no longer visible. He speaks about a "heaviness" in his stomach but regards this as a welcome symptom presaging relief. In a period ranging from thirty minutes to one hour, the muscular tremors disappear. He has become strong and well. He no longer walks with bowed head and stooped shoulders. He stands erect, is quite cheerful and lights his cigaret like any normal person. He becomes profuse in his apologies for his conduct during the abrupt withdrawal of the drug.

The intensity of some of these symptoms is undoubtedly subject to control on the part of the patient. We have stated that his mode of behavior is governed largely by his attempts to impress his suffering on those observing him. On the other hand, if there is a possible chance of obtaining his liberty from the ward he will state, though feeling ill, that he "feels fine," "has an excellent appetite" and is "sleeping well." He may have been successful in smuggling and administering the drug to himself and yet feign withdrawal symptoms so as to allay suspicion. When it is time for his discharge, he may feel well from the effects of the drug that he has been able to obtain through smuggling.

#### UNRELIABILITY IN RELATIONSHIP TO STUDY

This control of his symptoms on the part of the patient must be thoroughly understood by those engaged in the employment of various sorts of treatment. We believe that in many cases false conclusions are drawn as to the efficacy of a treatment if the value is deduced from the statements of the patient and his appearance. The scopolamine treatment that we have employed has always been stated by the patient who has been previously treated and who wishes to enter the ward to be "the best he has ever undergone, all others being torture." When he is just recovering from the effects of the scopolamine, it is "the worst," all others being excellent. When the time approaches for his discharge and he is anxious to obtain his liberty, the treatment again becomes the most successful he has ever had, he appears to have fully recovered his normal strength when he may still be so weak that he may not be able to walk several blocks without collapsing.

#### CONCLUSIONS

We have attempted in this paper to give a picture of the opium addict as we have found him in the wards of the Philadelphia General Hospital. We believe this description to be essential so far as it points out the difficulties encountered in the study of human addicts. Without this introductory paper, the reader might fail to appreciate in the papers which are to follow, the deceptiveness of the addict during experimentation.

# THE RADICULAR SYNDROME IN HYPERTROPHIC OSTEO-ARTHRITIS OF THE SPINE

AN ANALYSIS OF THIRTY CASES\*

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AND

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SAN FRANCISCO

Thirty-five years ago von Bechterew<sup>1</sup> wrote the first of a series of papers which described a syndrome consisting of stiff spine, nerve root pains, nerve root degeneration, alterations of sensation and muscle atrophies of a radicular distribution, which he ascribed to a pachymeningitis and compression of the nerve roots. Following the descriptions of Strumpell<sup>2</sup> and Marie<sup>3</sup> much discussion ensued on the classification of the various types of spondylitis, and with the exception of the work done in France and the reports by Camus<sup>4</sup>, Leri,<sup>5</sup> Sicard<sup>6</sup> and Barré,<sup>7</sup> the neurologic side of the syndrome has received little attention.

In the English and American literature references to the radicular syndrome have been few indeed, and under this title reference had not been made to spinal osteo-arthritis as the causative agent until the appearance of Rosenheck's<sup>8</sup> contribution in 1924 on radicular pain in spondylitis deformans. Well known textbooks<sup>9</sup> and systems of

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\* From the Department of Medicine, University of California Medical School

† Read in abstract before the General Medical Section at the Fifty-Seventh Annual Session of the California Medical Association April 30, 1928

1 Von Bechterew, W. Steifigkeit der Wirbelsäule und ihre Verkrümmung als Besondere Erkrankungsform, *Neurol Centralbl* **12** 426 (July 1) 1893

2 Strumpell, A. Bemerkung über die chronische ankylosierende Entzündung der Wirbelsäule und der Hüftgelenke. *Deutsche Ztschr f Nervenhe* **11** 338, 1897

3 Marie Pierre. Sur la spondylose rhizomelique, *Rev de med* **18** 285, 1898

4 Camus P. Étude de neuropathologie sur les radiculites. These de Paris, 1907-1908 p 26

5 Leri, Andre. La radiculite cervicale simple ou "Rhumatismale," *Bull et mem soc med d hôp de Paris* **40** 686, 1916

6 Sicard J A. Neurodocietes et funiculites vertebrales. *Presse med* **26** 9 (Jan 7) 1918

7 Barre, J A and Gunsett, A. Resultat de la radiotherapie dans 20 cas de radiculite par arthrite vertebrale (et en particuliere dans la sciaticque lumbosacree), *J de radiol et d'electrol* **5** 492, 1921

8 Rosenheck, C. Radicular Pain and Its Relation to Spondylitis Deformans from a Neurological Standpoint, *M J & Rec* **120** 215, 1924

9 Osler, Sir William, and McCrae T. The Principles and Practice of Medicine ed 9 New York D Appleton & Company 1923. Jelliffe, S F, and White, W A. Diseases of the Nervous System, Philadelphia, Lea & Febiger, 1923 p 445

medicine have rarely included the radicular syndrome or radiculitis in their indexes, but when included, the relation to osteo-arthritis of the spine has not been mentioned. Under discussions of spondylitis and of osteo-arthritis, Rhein<sup>10</sup> reported pathologic changes in nerve roots in a case of spondylose rhizomelique (P. Marie), Bailey and Casamajor<sup>11</sup> and also Parker and Adson,<sup>12</sup> noted pain and objective sensory disturbances from nerve root and cord compression, Danforth and Wilson,<sup>13</sup> observed the radicular nature of sciatica, and Rosenheck,<sup>14</sup> called attention to so-called meralgia paraesthetica as a radicular manifestation. Osler,<sup>15</sup> under the heading of spondylitis, quoted von Bechterew's original observations, and McCrae,<sup>16</sup> in the Oxford System of Medicine, stated that "sensory changes are important," but, like many other writers, he left the reader rather doubtful regarding their nature and distribution.

Radiculitis may be described as an acute inflammation of the spinal nerve roots, manifested by alterations of sensation or of changes in muscle function, which show by their distribution that the primary disease process is in the spinal root and not in the tracts and nuclei of the cord, or in a peripheral nerve trunk. Dejerine<sup>17</sup> considered syphilis and tuberculosis the most common etiologies. Spinal osteo-arthritis as a cause of radiculitis received little attention.

A root type of altered sensation or of changed motor power is not distinctive in itself, because a similar picture may be produced in many diseases of the spine. That radiculitis may result from osteo-arthritis of the spine and is due to involvement of the nerve root, either from the meningeal reaction secondary to the osteo-arthritic process, or from pressure in narrowed canals, has been shown experimentally by Nathan,<sup>18</sup>

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10 Rhein, J. H. W. Pathologic Report of the Nervous System in a Case of Spondylose Rhizomelique, *J. A. M. A.* **51** 463 (Aug. 8) 1908.

11 Bailey, P., and Casamajor, L. Osteoarthritis of the Spine as a Cause of Compression of the Spinal Cord and Its Roots, *J. Nerv. & Ment. Dis.* **38** 588, 1911.

12 Parker, H. L., and Adson, A. W. Compression of the Spinal Cord and Its Roots by Hypertrophic Osteoarthritis. Diagnosis and Treatment, *Surg. Gynec. Obst.* **41** 1, 1925.

13 Danforth, M. S., and Wilson, P. D. Anatomy of the Lumbo-Sacral Region in Relation to Sciatic Pain, *J. Bone & Joint Surg.* **7** 109, 1925.

14 Rosenheck, C. Meralgia Paraesthetica. Relation to Osteo-arthritis of Spinal Vertebrae, *J. A. M. A.* **85** 416 (Aug. 8) 1925.

15 Osler (footnote 9, first reference).

16 McCrae, Thomas. Arthritis Deformans, Oxford Medicine, London, Oxford University Press, vol. 4, p. 390.

17 Dejerine, J. Semiologie des affections du système nerveux, Paris, Masson & Cie, 1914, pp. 257 and 821.

18 Nathan, P. W. The Neurological Condition Associated with Polyarthritis and Spondylitis, *Am. J. M. Sc.* **152** 667, 1916.

and recognized clinically and described by certain French workers,<sup>19</sup> as rheumatic radiculitis, neurodocitis, funiculitis and funicular-radiculitis. But even as late as 1922, Bassoe,<sup>20</sup> in discussing nerve syndromes and osteo-arthritis of the spine as a cause of sciatica, lumbago and cervical, brachial and intercostal neuralgias, called attention to the appalling lack of objective observations.

There are no criteria by which the extrameningeal neurodocitis or funiculitis of Sicard<sup>6</sup> (fig 1) can be distinguished from the involvement of the intrameningeal portion of the root, since the involvement of either part will be manifested as a radicular disturbance.<sup>21</sup> In this study, therefore, to denote involvement of the spinal nerve roots we shall use the terms radicular syndrome or radiculitis. These will include the extrameningeal funiculitis and intervertebral neurodocitis of Sicard, and the intrameningeal radiculitis of Dejerine.

Mayer<sup>22</sup> indicated that there may not be any demonstrable sensory changes in the early stages of radiculitis, and that later disturbances consist of alterations in light touch. Osteo-arthritis of the spine is a common disease indeed, and from the very nature of the process radicular manifestations with sensory changes to light touch should be present.

#### ANATOMY

The spinal nerves are joined to the spinal cord by their dorsal and ventral roots, which are frayed-out bundles of axons, called the fila radicularia, at their lines of attachment to the cord. The fila radicularia and the short intrameningeal portions of the roots are called by Sicard the "radicular nerves," as distinguished from the extrameningeal portions which he calls the "funicular nerve" (fig 1). The dorsal root contains the spinal ganglion (fig 2), which is closely invested by the dura mater, but is largely outside its cavity.

Although the roots pierce the dura separately, they are enclosed in a single tubular sheath of dura, which includes the spinal ganglion and posterior root, and thus ensheathed, the spinal nerve occupies the intervertebral foramen. The ganglions of the last lumbar and first four sacral nerves lie inside the vertebral canal, but outside the dural sac, while the ganglions of the last sacral and the coccygeal nerves lie not

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19 Camus (footnote 4) Leré (footnote 5) Sicard (footnote 6) Barre and Gunsett (footnote 7)

20 Bassoe, P. Nervous Syndromes. Osteoarthritis of the Spine, Vertebral Funiculitis Neurodocitis, *Internat Clin* 3:232, 1922.

21 Williams, T. A. Differential Diagnosis of Radiculitis and Neuritis, *Arch Diagnosis* 14:140, 1922.

22 Mayer, E. E. Radiculitis. Its Diagnosis and Interpretation, *J. A. M. A.* 71:353 (Aug. 3) 1918.

only inside the vertebral canal, but inside the dural sac as well. The two roots leave the intervertebral foramen together as a short trunk which soon breaks up into branches, which in certain regions furnish the elements making up the plexus (fig 1). The dura is separated from the periosteum and the wall of the intervertebral canal by a very small interval, containing thin-walled plexiform veins and loose fatty connective tissue.<sup>23</sup>

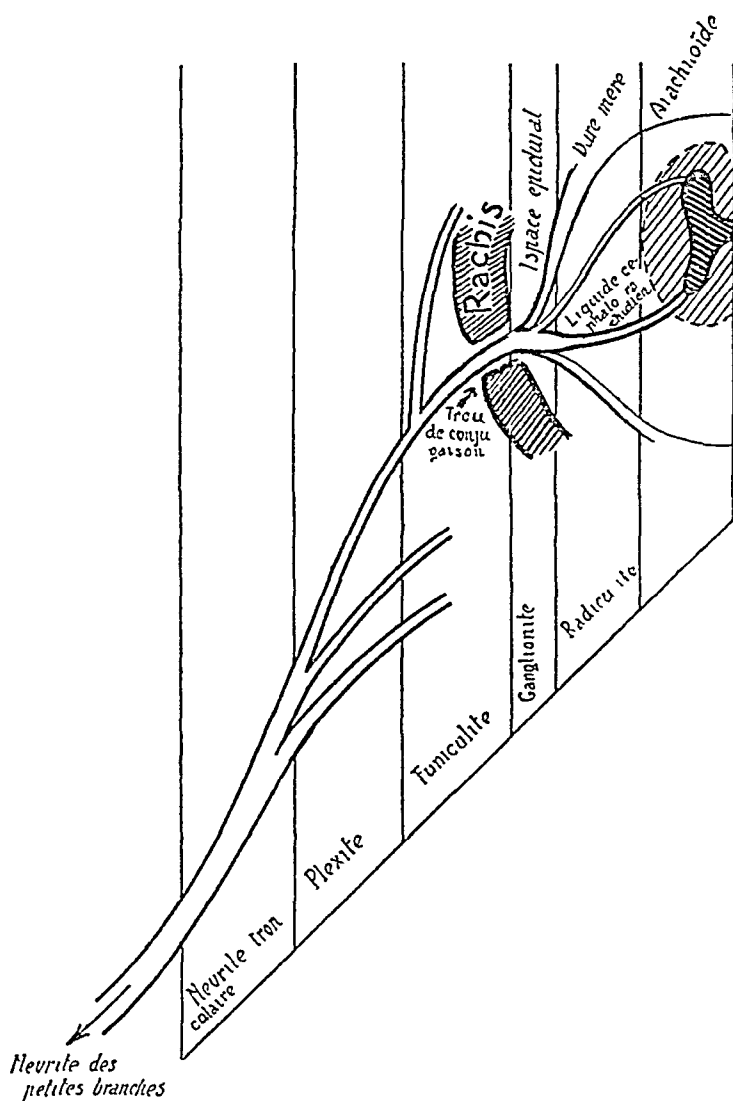


Fig 1—Sicard's schematic representation of the spinal roots. He called the *fila radicularia* and the short intrameningeal portions of the spinal root the "radicular nerve", the extrameningeal portion the "funicular nerve," and the intervertebral foramen the "neurodocha".

Sicard<sup>6</sup> used the term "neurodocha" to describe the bony canal through which the spinal roots pass to reach their foramina of exit (fig 1). A pathologic process within the intervertebral canal (the

<sup>23</sup> Robinson, Arthur. Cunningham's Text-Book of Anatomy, ed 5, New York, William Wood & Company, 1923, pp 711-713.

neurodocha), he called a neurodocitis and involvement of the short extrameningeal spinal root trunk (the funiculite), he termed a funiculitis. Sensory alterations (or changes in motor power), dependent on a pathologic process in a given nerve root, will be manifested at the periphery as a radicular disturbance (fig 3) regardless of whether or not the part involved is intrameningeal or extrameningeal<sup>22</sup>

The spinal roots vary in size. The largest are those that take part in the formation of the great nerve trunks of the limbs, namely, the lower cervical and first thoracic roots and the lumbar and sacral roots

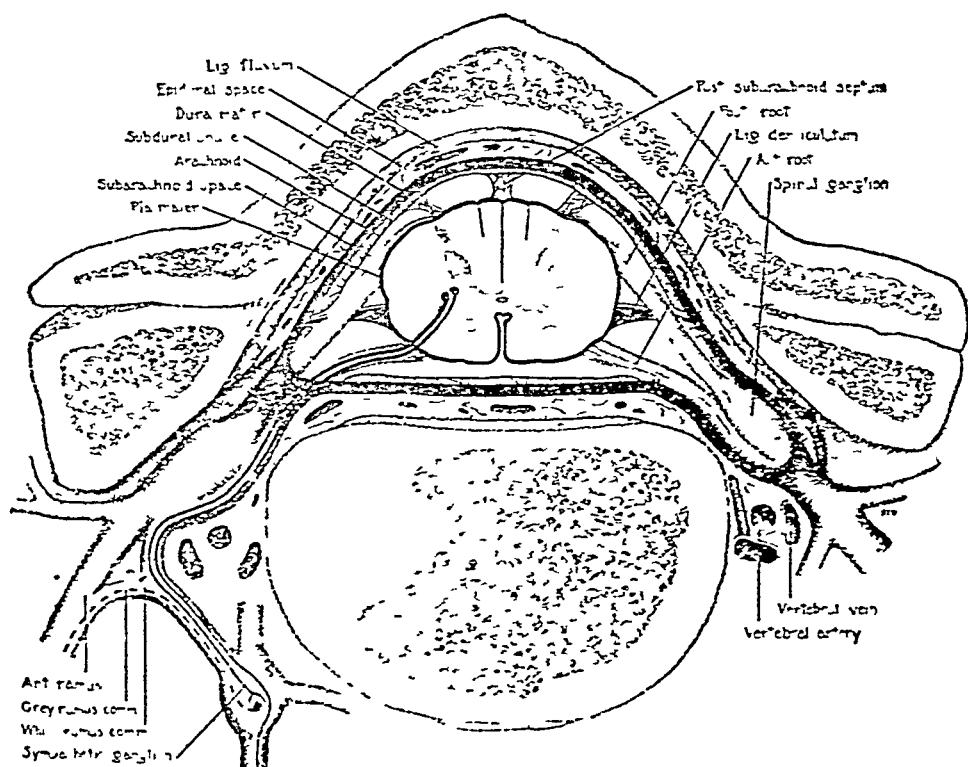


Fig 2—The spinal nerve roots and meningeal sheaths (From Mayer [foot-note 22] )

Of these, the nerves destined for the lower limbs are the larger. All the thoracic nerves except the first are small<sup>23</sup>

The sixth cervical root is the largest of the cervical nerves<sup>24</sup>. These roots diminish in size from below upward<sup>23</sup>. The size of the nerve root in relation to the canal is of definite importance in determining the liability to mechanical irritation. Danforth and Wilson,<sup>13</sup> in a careful study by dissection of the lumbar and sacral nerves, found that beginning with the fifth lumbar root, from below upward, the size of the nerve decreased relatively to the size of the foramen, viz, for their size

<sup>24</sup> Pierson, G. A. Human Anatomy, Philadelphia J. B. Lippincott Company, 1907, vol 2, p 1279

the fifth lumbar roots had the smallest canals, frequently almost filling them, the fourth lumbar roots rarely completely filled the foramina of exit, and the second and third lumbar roots never completely filled the openings

With respect to the size of individual roots, the posterior are larger than the anterior. They contain a greater number of radicular fibers, and the individual fibers are larger.<sup>23</sup> In the cervical region, the posterior

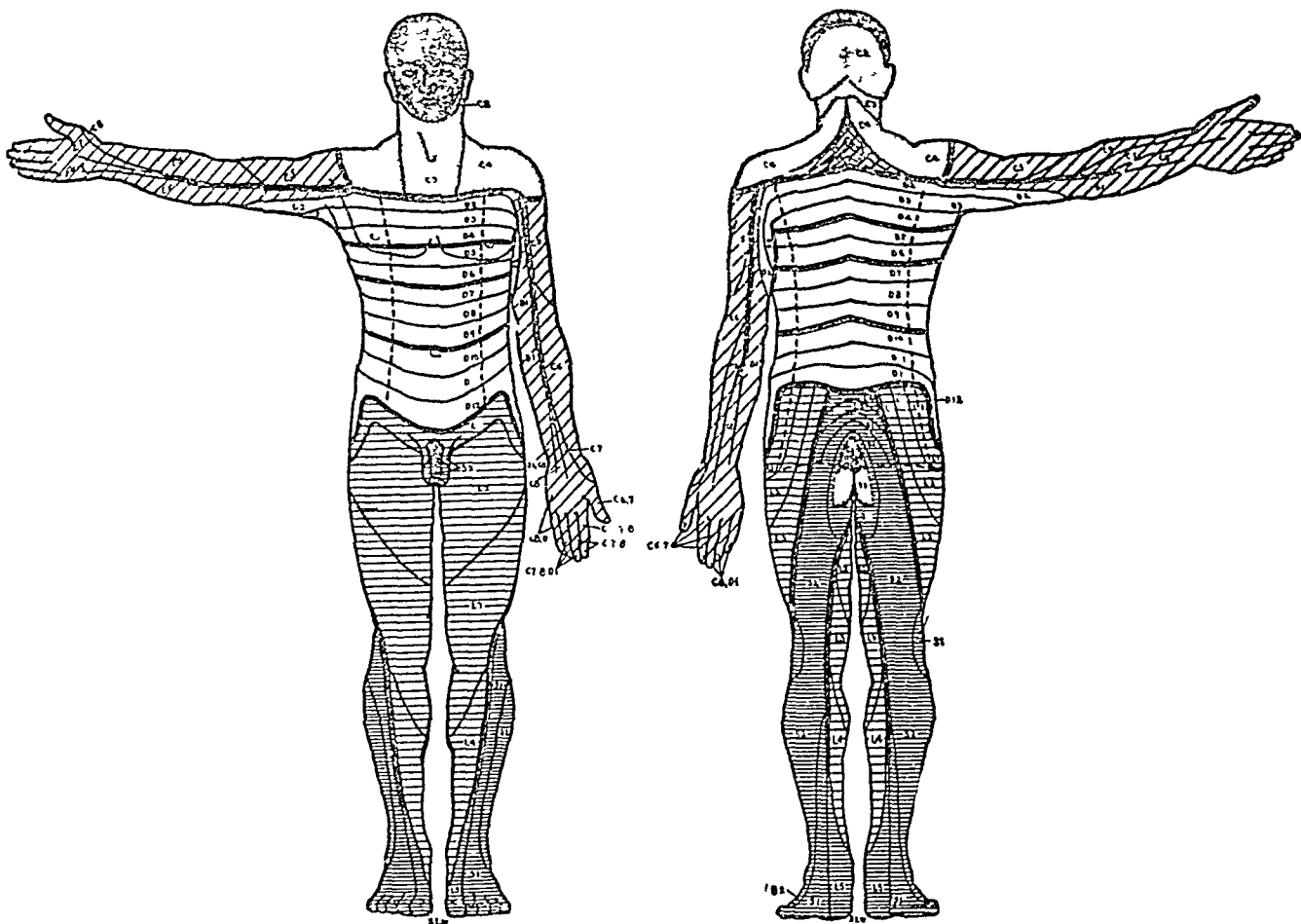


Fig 3—The topographic distribution of the spinal nerve roots. Radicular sensory innervation: heavy lines indicate direction or axial lines (modified from Dejerine and Flatau). (From Mayer [footnote 22].)

roots are three times larger than the anterior,<sup>25</sup> except in the case of the first cervical, which is always smaller, and, in rare cases, absent.

The composition of the intervertebral canal and the relation of the roots in this canal are of some importance. The roots are in relation, above and below, respectively, to the inferior and superior intervertebral notches of the adjacent vertebrae, in front, with some of the posterior part of the bodies and with a portion of the intervertebral disk separat-

<sup>25</sup> Lewis, W. H. Gray's Anatomy, ed 21, Philadelphia, Lea & Febiger, 1924, p 923.



ing them, and behind, is the posterior articulation. The superior posterior articular facet reaches upward toward the inferior intervertebral notch of the body above, and on movements of extension it approaches the nerve root in the canal and further decreases the size of the intervertebral foramen.<sup>13</sup>

#### ETIOLOGY, PATHOLOGY AND PATHOGENESIS

Von Bechterew found a pachymeningitis and degeneration of the nerve roots. He considered the neurologic symptoms due to this pathologic condition, with consequent mechanical compression of the nerve roots. Various French writers, Chapault and Raymond (cited by Camus<sup>4</sup>), Leri<sup>5</sup> and Sicard,<sup>6</sup> conformed essentially to this view. Leri, particularly, indicated the possibility of the process being inflammatory. Sicard considered the process periosteal inflammation with secondary involvement of the meninges of the nerve roots in the intervertebral canal. Bailey and Casamajor<sup>11</sup> described in considerable detail the gross pathologic changes of advanced spinal osteo-arthritis, and stressed particularly the thickened root meninges and bony overgrowths from the posterior surfaces of the vertebral bodies and around the intervertebral canal as a cause of compression of the cord as well as the roots. Like their predecessors,<sup>26</sup> they felt that symptoms were produced by mechanical irritation and pressure on the nerve roots in the intervertebral foramen. Rhem<sup>10</sup> found nerve root and muscle degeneration in a case of spondylose rhizomlique (P. Marie). This observation is essentially the pathologic picture described originally by von Bechterew.

In this country, Nathan,<sup>18</sup> by experimental work on dogs and comparative studies of the pathologic changes in man, called attention to the inflammatory nature of the pathologic process in spondylitis deformans. He concluded that subjective and objective sensory alterations of a radicular nature should be present, depending in degree on the severity of the periradicular exudation. The intensity and permanence of these symptoms depended on the fibrosis subsequent to repair after the inflammatory process had subsided. The persistence of neurologic symptoms and signs were due, he thought, to a mechanical disturbance in the spinal canal and in the intervertebral foramen, secondary to these sequellae. Patrick<sup>27</sup> stressed the occurrence of low grade fever and low grade leukocytosis in osteo-arthritic processes. Elliott<sup>28</sup> discussed Nathan's work and the theories advanced as to the etiology of spinal osteo-arthritis.

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26 Bechterew (footnote 1) Camus (footnote 4) Leri (footnote 5)

27 Patrick, H. T. Neuritis and Sciatica, *J. A. M. A.*, 69 2176 (Dec. 29) 1917

28 Elliott, G. R. Spinal Osteoarthritis Involving Cervical Region, *J. Bone & Joint Surg.* 8 42, 1926

The similar observations of von Bechterew and Rhein in supposedly different types, would indicate that the pathologic condition of the nerve roots was essentially the same in the various forms of spondylitis. Nathan felt that it was unnecessary to classify spondylitis according to the presence or absence of neural symptoms, the mode of progression or the involvement of ribs and joints of the extremities. "Whether or not these parts are involved is merely an accident of location of a generalized process, and such accidental distribution provides the forms commonly associated with the names of von Bechterew, Strumpell, P. Marie, etc. These conditions are not essentially different—like all inflammatory conditions they may be acute, chronic, transient, or progressive, with or without permanent changes to the tissues involved."

Parkei and Adson,<sup>12</sup> in a series of patients with nerve root and cord symptoms, who were subjected to exploratory laminectomy, found that the hypertrophic process may be extensive without roentgenologic evidence of its presence. They too concluded that the process was inflammatory, with infection and trauma as the prominent factors. The former they considered the more common and prominent cause of the disease, and the latter the predisposing factor, which continued the process through mechanical irritation.

#### METHOD OF STUDY

In the medical out-patient department and wards of the University of California Hospital, studies were conducted on patients whose symptoms indicated disturbances of the spinal roots. In the history of the chief complaint, the patients outlined the painful areas lying in a root, or a group of roots, to a degree that was remarkable for its topographic accuracy. When they were questioned, the history brought out that there had been other painful areas of spinal root distribution not complained of at the time. The demonstration of root involvement was equally consistent, when analysis was made of the past history of patients without subjective complaints, in whom moderate to marked hypertrophic changes were found by x-ray examination. In either event, the history of the involvement of various spinal root areas was obtained, and from it a record of involved roots could be formed, which, in most cases, was sufficiently accurate in itself to suggest the levels at which a pathologic process might be anticipated in the spinal vertebrae.

Alterations in sensation to light touch were tested for on all patients by the use of the cotton tuft on a wooden applicator which was approximately 6 inches (15.24 cm.) long. The applicator was held lightly at about its midpoint, and the tufted end was applied to the skin, resting by its own weight without added pressure from the hand. In

a number of patients, tests were conducted with the pinpoint, heat, cold and pinching. One or two painful areas were selected at a given examination, usually that of chief complaint, and other regions were left for a later examination. This procedure was adopted because of the patient's ready fatigue incident to examination for alterations in light touch. Several examinations were necessary if all the involved areas were to be studied.

#### AGE AND SEX INCIDENCE

*Age*—The age incidence of hypertrophic osteo-arthritis of the spine covers a wide range. It is not necessarily a part of old age. The youngest patient in this series showing x-ray evidence of spinal osteo-arthritis was 34, and the oldest was 72. Twenty-three patients were between the ages of 37 and 54, and five patients were over 55.

*Sex*—Hypertrophic osteo-arthritis of the spine is considered to be more prevalent in men than in women,<sup>12</sup> the reason given being that in men the spine is subject to more trauma. In this group, the women outnumbered the men two to one. This reversibility may be explained by the attendance figures at the afternoon clinic of the University of California Medical Dispensary, where most of this work was carried on. In attendance, the women outnumbered the men in about the same ratio.

#### SINGLE SYMPTOMS AND REGIONS INVOLVED

In order of frequency, the chief complaints were pain, aching, soreness, stiffness, paresthesia (burning, numbness, tingling, heaviness, weight), dizziness, cramps and tenderness. Pain was described as sharp, shooting, gnawing, catching, tender, dull, pinching, twinging, piercing and the like, in various ways, according to the manner of expression of the patient. Aching was of a dull character, and the soreness was either heavy or light. The outstanding symptoms, according to frequency, were pain, aching, soreness, and stiffness.

The regions complained of (fig 4), according to frequency, were (1) an area immediately over the sacrum with sciatic radiation (fig 4A), (2) localized pain over the sacrum, with concomitant pain on the inner side of the legs (fig 4B), (3) an area over the back of the neck (fig 4C), (4) the side of the neck and shoulders (fig 4D), (5) over the occiput and vertex (fig 4F), (6) the upper part of the abdomen and the epigastrium, with radiation to the back (fig 4G), (7) the lower part of the abdomen, with radiation to the back, or from the back (fig 4H), (8) the precordium with radiation to the inner part of the left arm (fig 4I), and (9) the outer side and front of the thigh (fig 4J). Although the patients complained of pain on one side more than on the other, bilateral involvement was most frequent, the right side receiving more attention in the abdomen and

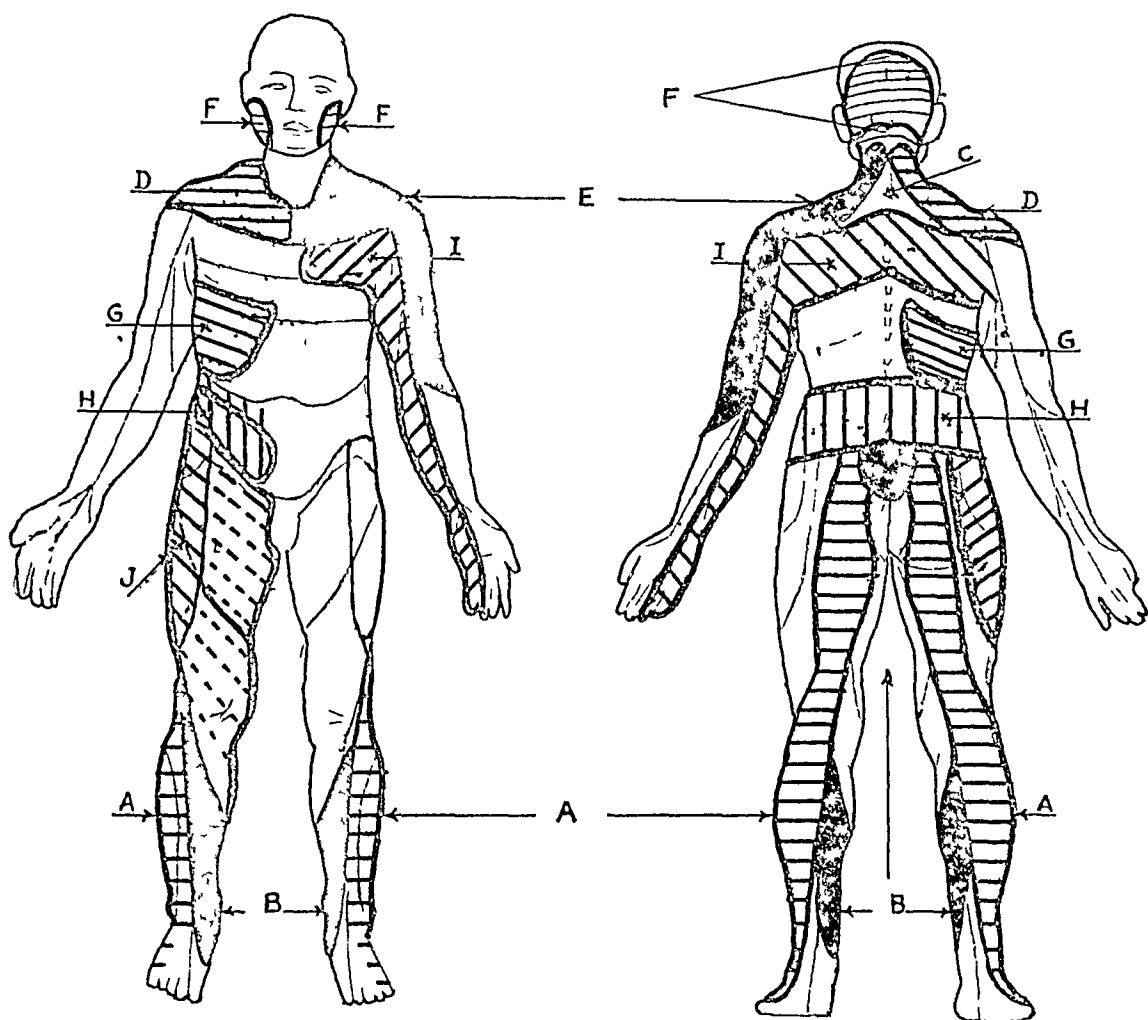


Fig 4—A, the radicular distribution of the sacral roots 1 and 2, "sciatica" B, the radicular distribution of the lumbar roots 4 and 5 and the sacral root 1 over the sacrum (backache) and the radicular distribution of the lumbar root 4 on the "inner side of the legs" C, the radicular distribution of the cervical roots 5, 6 and 7 over the area "up and down the back of the neck" D, the radicular distribution of the cervical root 4 over the "side of the neck" and the "shoulder" E, the radicular distribution of the cervical root 4 and radiation "over the arm" found when areas D and E were affected concomitantly F, the radicular distribution of the cervical roots 1, 2 and 3 over the back of the head and neck and on the face Spoken of as "headache" by the patient, occipital and vertex G, the radicular distribution of the dorsal roots 6, 7, 8 and 9, the area of referred pain in disease of the gallbladder H, the radicular distribution of the dorsal roots 10, 11, and 12, the area of referred pain and local tenderness in appendicitis, also backache over the "small of the back" I, the radicular distribution of the dorsal roots 1, 2, 3, 4 and 5, the area of referred pain in certain cardiac diseases J, the radicular distribution of the lumbar roots 1, 2 and 3 on the outer side of the thigh (may be confused with meralgia paraesthetica) and across the front and inner side of the thigh

the left side over the upper part of the chest. Questioning was sometimes necessary to bring out the bilateral nature of the symptoms.

The roots which make up the great nerves of the lower and upper extremities were outstandingly involved, when the location of the symptoms was noted according to their frequency. The involvement of the roots supplying the lower extremities was somewhat more frequent than of those to the upper extremities. The incidence of involvement can be explained by anatomic facts. The roots forming the great nerve trunks of the lower extremities are the largest of all the spinal roots. Those supplying the cutaneous distribution of so-called sciatica, the fourth and fifth lumbar and the first two sacral roots, are most frequently subjected to mechanical irritation or compression owing to narrowed canals caused by arthritis of the fourth and fifth lumbar vertebrae, and of the lumbosacral and sacro-iliac joints<sup>13</sup>. The less frequent radicular symptoms and sensory changes in the upper lumbar roots in this series of cases may be explained by the fact that the first, second and third lumbar roots rarely fill their containing canals by one half and are, therefore, less apt to be affected by processes tending to decrease the relative size of the intervertebral canal<sup>13</sup>.

In the cervical region, symptoms referable to the lower cervical roots were twice as frequent as those to the upper. This may be explained by the diminishing size of the cervical roots from below upward, the sixth cervical root being the largest<sup>24</sup>. The nature of the cervical curve and the greater mobility of the lower cervical vertebrae increased the liability of these roots to mechanical irritation.

In the abdomen, symptoms over the right upper and right lower quadrants received more attention than the corresponding left quadrants. The dorsal roots are small, everything else being equal, the greater mobility of the lower dorsal vertebrae enables mechanical trauma to play a greater rôle in the corresponding dorsal roots. Education of the laity, by the medical profession, and by surgeons in particular, concerning diseases of the gallbladder and the appendix, has perhaps caused attention to be focused on these regions, for, despite bilateral symptoms, the patients seemed more concerned with disturbances on the right side of the abdomen. That the location of a known organ draws attention to one side of the body is well illustrated in the upper part of the chest where the painful area, in the proximity of the heart, attracted overwhelming attention to the left side. There was a tendency to minimize the pain on the right side of the chest. When a patient was asked if he would seek a physician because of pain on the right side, such as he now felt on the left side, it was quite characteristic to have him reply "I would pay no attention to it because the heart is not on that side."

## THE COMMON SYMPTOMS IN THE INVOLVED REGIONS

*Fingers*—Paresthesias were the main symptoms. These, in order of frequency, were tingling, numbness and anesthesia. They were associated with the involvement of the lowermost cervical and the upper dorsal vertebrae.

*Head*—Headache was the chief complaint. It was usually described as a dull ache, soreness or burning, at the occiput, which shot most commonly to the vertex, and less frequently around the side of the head to the temples. The subjective sensations at the vertex were those of piercing pain, tenderness, soreness, burning or a dull ache (fig 4F). These symptoms were associated with the involvement of the second or third cervical vertebrae, or both.

*Back of the Neck*—Pain, aching, soreness and stiffness up and down the back of the neck from the cervical prominence (less frequently between the upper part of the shoulder blades) up to the occiput were the outstanding symptoms of this region. The sensation of a lump over the cervical prominence and, less frequently, of paresthesias, such as numbness, burning and tightness, were also symptoms (fig 4C). These were associated with the involvement of the fifth and sixth or seventh cervical vertebrae.

*Shoulders*—In this region, the symptoms consisted of pain, or aching, and soreness on the outer side of the neck. Radiation occurred outward over the shoulders and was described as "painful shoulders," or to the front of the chest as far down as the second interspace (excluding the space on the neck between the bellies of the sternomastoid) (fig 4D). Stiffness of the shoulders was less frequently a symptom. Occasionally, there was a complaint of paresthesia, such as burning and tightness. When arthritis of the shoulder was present concomitantly with cervical arthritis, clackling in the shoulder joint was an added symptom. When symptoms over the back of the neck and the shoulder areas coexisted, radiation occurred from the side of the neck and shoulder to the outer side of the arm, and often to the base of the thumb (fig 4E). These symptoms were described as pain, aching or heaviness. The osteo-arthritic process was found in the fourth, fifth and sixth or seventh cervical vertebrae, or the fifth and sixth cervical vertebrae alone, when the upper and posterior border of the fifth vertebra also showed arthritic changes.

*Upper Part of the Chest (Precordium, Mammary Region)*—Pain and aching over the precordium (second to fourth or fifth interspace) were outstanding symptoms. Pain, when acute, was sharp (like pins), and between acute episodes it was described as dull or aching. Radiation occurred to the armpit and down the inner side of the arm, often to the fingertips (fig 4I). When symptoms were most pronounced on the left

side the patient frequently associated them with the heart, and, in certain introspective persons, tachycardia and fear of breathing would follow. Less frequently, symptoms of soreness and paresthesias, such as numbness and burning, were described. These symptoms were associated with the involvement of the upper four or five dorsal vertebrae.

*Upper Part of the Chest (Between the Shoulders)*—Soreness between the shoulders was practically the only complaint in this region, and existed usually as an extension of symptoms from the area up and down the back of the neck, or in conjunction with symptoms across the upper part of the chest, when the upper dorsal vertebrae were involved (figs 4I and 5).

*Lower Part of the Chest (Hypochondrium)*—In the hypochondrium the symptoms were pain or aching with radiation to either side, along the costal margin to the shoulder blade, or heaviness, stabbing pain, pressure and "gas" across the epigastrium. Such symptoms on the right side were over the area of distribution of the referred pain of disease of the gallbladder (fig 4G).

*Epigastrium*—Pain and paresthesias, such as burning, tingling and heaviness, pressure, stabbing pain and "gas," were the symptoms in order of frequency. These extended bandlike across the epigastrium, or radiated across the hypochondrium, on either side, along the costal margin to the shoulder blade, as previously described, or as a girdle pain and aching across the navel. The latter would be referred to the upper part of the small of the back, just below the angles of the scapulae (fig 4G). Symptoms in these areas were associated with the involvement of the middorsal vertebrae.

*Lower Part of the Abdomen*—Pain, aching and stabbing were the main symptoms (the latter symptom usually occurred in the right lower quadrant), and, less frequently, soreness and burning. These were usually referred to the small of the back, or began posteriorly, and were referred from the small of the back where stiffness and weakness were occasional symptoms (fig 4H). They were associated with the involvement of the three lower dorsal vertebrae.

*Inguinal Ligament, Side of the Thigh and Upper Front Part of the Thigh*—Pain, burning or aching, starting over the upper outer aspect of the thigh, at or behind the crests of the ilium, were the main symptoms of the patient's chief complaint. Radiation occurred into the area over the inguinal ligament, or across the front of the thigh to the inner aspect and downward to the knee and, less frequently, to the inner side of the leg. Questioning was often necessary to determine the distribution of the radiation. Tenderness to pressure, below the lateral part of Poupart's ligament, was occasionally present (fig 4J). Symp-

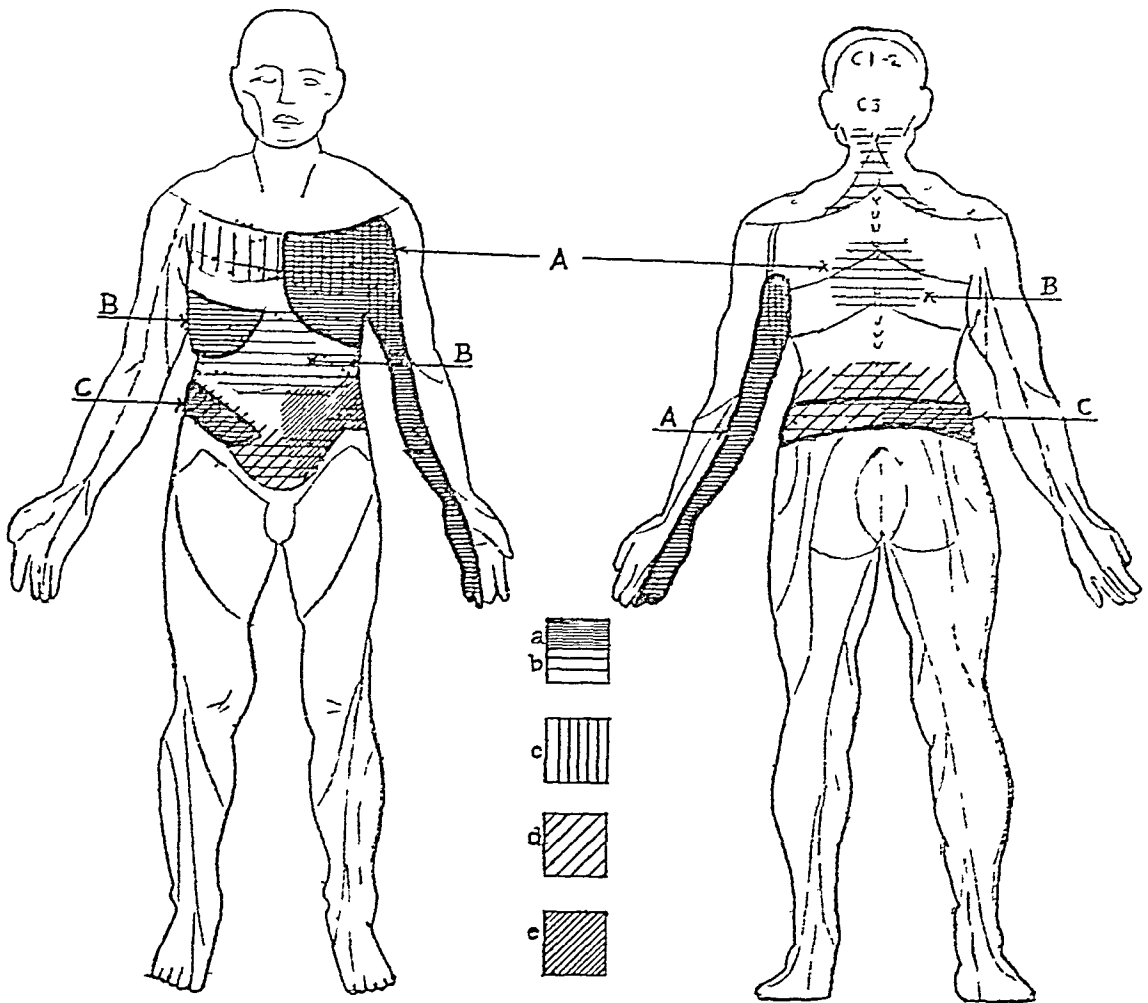


Fig 5 (case 5) —Illustrating pseudo-ang na pectoris, pseudo-appendicitis, gastric disturbances and pseudocholecystitis *A*, the radicular distribution of the dorsal roots 1, 2, 3, 4, 5 and 6, subjective sensory disturbances for a period of twelve years, acutely for five months, disturbances worse on the left, mistaken diagnosis of angina pectoris *B*, the radicular distribution of the dorsal roots 6, 7, 8 and 9, subjective sensory disturbances over a period of twelve years, worse on the right, associated with the "stomach" by the patient, diagnosis of chronic cholecystitis and investigation for disease of the gallbladder was made *C*, the radicular distribution of the dorsal roots 10, 11 and 12, subjective sensory disturbances for several years, symptoms greatest on the right, a diagnosis of chronic appendicitis was made, the surgeon advised appendectomy, area of backache over the "small of the back" *a*, subjective sensory disturbances, area of chief complaint, *b*, subjective sensory disturbances, other areas brought out in the past history, *c*, moderate increase in sensation to the cotton tuft, *d*, moderate decrease in sensation to the cotton tuft, *e*, marked decrease in sensation to the cotton tuft



toms in this area were associated with the involvement of the upper lumbar vertebrae above the third lumbar vertebra

Symptoms on the inner side of the leg were more often associated with symptoms of localized pain over the sacrum (fig 4B) The latter pain will be explained fully later

*Over the Sacrum*—Pain was the outstanding symptom in this area As a symptom, localized pain over the sacrum (backache) was often present along with pain on the inner side of the leg The patient spoke of backache, but closer scrutiny revealed a localization to the area over the sacrum Most frequently, the pain radiated down the posterior middle part of the thigh to the popliteal space (the peripheral distribution of the posterior cutaneous nerve of the thigh), thence to the outer side of the leg to the dorsum of the foot (the peripheral distribution of the external popliteal nerve) (fig 4A) Paresthesias, such as numbness and tingling over the posterior surface of the thigh and over the dorsum of the foot, were less frequent symptoms Sciatic pain was associated with the involvement of any of the following the third lumbar vertebra, the lumbar vertebrae below it, a sacralized transverse process of the fifth lumbar or arthritic changes about the sacro-iliac joint

#### GENERAL SYMPTOMATOLOGY, FACTORS WHICH INDUCED OR AGGRAVATED SYMPTOMS

The cardinal symptoms were pain, aching and soreness, brought on or aggravated by the movement of the spinal column The most common factors that induced or aggravated the symptoms were sneezing, straining at stool, coughing (Dejerine's sign), rising after a sitting position, raising the head on awakening, getting out of bed, walking, sitting in one place for any length of time, a change of position and lifting Pain at night, which awakened the patient and was relieved by a change of position was commonly noted Inability to sit up in bed from a supine position, without producing pain, and the necessity of rolling out on one side or the other were quite characteristic Many of the patients preferred a hard bed, obtaining most rest when lying flat on the back The wearing of a corset, strapping, heat and massage were measures that gave relief

Pain, induced or aggravated by movement of the spine, as described before, in some form or other, was common to all cases Dejerine's sign (coughing, sneezing and straining at stool) occurred first as the single factor which aggravated the symptoms in all the regions of the spine The presence of this sign is useful but does not indicate the cause<sup>22</sup> The acts, which constitute Dejerine's sign, outstandingly affected the back of the neck and shoulder regions, the area over the sacrum and the so-called sciatic distribution In the neck, sneez-

ing induced symptoms oftener than coughing or straining, and over the small of the back and sacral regions, straining at stool was more often an aggravating factor. It is noteworthy that sneezing affected the upper spinal roots more than straining at stool, and the latter, in turn, affected the lower spinal roots. This may be explained by the mechanics of the acts involved. The acts that constitute Dejerine's sign cause an increase in intraspinal pressure and probably act mechanically on the roots and the meninges of the roots. The latter have already lost their elasticity incidental to sequelae of the osteoarthritic process.<sup>20</sup>

Coughing is the least aggravating factor of the three that constitute Dejerine's sign. In the absence of pulmonary infection, coughing is ordinarily done lightly, as in clearing the throat. No doubt, if coughing were indulged in severely enough to raise the intraspinal pressure to the same degree as occasioned by sneezing and straining at stool, symptoms might be induced and aggravated to as great a degree. All regions were particularly affected by any position that induced relaxation of the protecting muscles, such as lying in bed and prolonged sitting in one position.

Pain, as seen in this study, was a bothersome symptom and sometimes troublesome enough to interfere with work. It was not, as a rule, severe and not in any instance was it extreme enough to require opiates. It lacked the severity of the pain seen in Pott's disease and in tumors of the vertebrae and cord. The spontaneity seen in the latter condition was not present. Movement, of the Dejerine sign, was always the provoking factor. Localized vertebral pain and tenderness, as seen in Pott's disease and new growths of the vertebrae or cord, were not present. While pain was a symptom which appeared at night and interrupted the patient's sleep, in no case did the patient walk the floor or sleep in a chair for relief. This symptom appears in new growths of the cord and vertebrae, and has been stressed by Parker and Adson.<sup>12</sup> In fact, in our patients such maneuvers invariably aggravated symptoms.

#### SENSORY ALTERATIONS

For the most part, the sensory changes were bilateral in distribution. The most common observations were hyperesthesia, hypesthesia or anesthesia to the cotton tuft. When hypesthesia to the cotton tuft was marked, a slightly decreased sensibility to the pinpoint was also found to be present. In a given patient, altered responses to heat and cold were in the same direction as those elicited with the cotton tuft or the pin.

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29 Bechterew (footnote 1) Bailey and Casamajor (footnote 11) Nathan (footnote 18)

Hyperesthesia to the cotton tuft was commonly found in patients with complaints dating within one year. Occasionally, a patient with symptoms of many years' duration suffered an acute attack in a given region. Hyperesthesia was found when the exacerbation of symptoms was of less than one year's duration. In the areas supplied by the lower cervical roots, and the lower lumbar and upper sacral roots, hyperesthesia was occasionally found in patients with symptoms of five or more years' duration. Hypesthesia to the cotton tuft was common in patients whose symptoms extended beyond a period of five years, and occasionally could be found in cases in which the symptoms were of less than three or four years' duration. Marked hypesthesia to the cotton tuft, anesthesia to the cotton tuft and slight hypesthesia to the pin stroke were generally found in patients with symptoms of more than five years' duration and rarely in patients with symptoms of between three and five years' duration<sup>30</sup>

Sensory disturbances varied in extent, severity and character, from a small area of hyperesthesia to a sensorium dulled to light touch over most of the body. Such alterations in the sensation of light touch were found constantly, and it became possible, after a number of examinations to chart out the entire body and to anticipate from the chart the levels of the spinal vertebrae at which pathologic processes might occur.

*X-Ray Changes*—In the well marked hypertrophic process, the presence of spurs on the anterior and lateral parts of the bodies of the vertebrae requires little comment. Hypertrophic spurs were also noted on the posterior margins of the vertebrae. Fluffiness and fuzzy projections were noted along the margin of the bodies in certain cases, which we believe indicate the earlier x-ray changes of hypertrophic spinal osteoarthritis. Loss of the intervertebral disk substance was noted particularly in those patients who showed abnormal bowing of the spinal column, and was seen especially in the dorsal vertebrae. In the extremely marked process, a certain degree of atrophy of the bodies of the vertebrae was noted. Calcification of the anterior ligaments that appeared as though molten bone had been poured over several of the vertebral bodies without apparent loss of intervertebral disk substance, was seen in two patients who elsewhere in the spine showed the more common spur formations. The varied changes observed were associated with nerve root symptoms and alterations of sensation at the particular vertebral level that was involved.

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30 In patients studied since this series was analyzed, the A and B pinching tests of Carnett (Carnett, J. B. *Intercostal Neuralgia as the Cause of Abdominal Pain and Tenderness*, Surg Gynec Obst 42:625 [May] 1926) were found useful when marked hyperesthesia and hyperalgesia were present over the abdomen.

## BLOOD PRESSURE

Hypertension was not a prominent observation in this study. In twenty-four patients, the readings for the systolic blood pressure varied between 100 and 150. In five patients, the readings for the systolic blood pressure varied between 154 and 162. One patient had a systolic blood pressure of 184.

In twenty-six patients, the readings for the diastolic blood pressure varied between 66 and 80. For the remaining four patients of the series, two diastolic readings were obtained at 98 and 102 and two at 120 and 124.

## RESUME

As may be seen from the foregoing facts, the symptomatology may be diffuse, depending on the vertebral levels involved. Cervical involvement is associated with headache, sore neck, painful shoulders and arms. Upper dorsal involvement is associated with precordial pain, which is considered by the patient, and often by his physician, to be of cardiac origin. Pain in the epigastrium and over the region of the gallbladder was noted when the mid-dorsal vertebrae were involved. Pain over the lower part of the abdomen, which required a differential diagnosis from appendicitis and pelvic disease, was associated with the involvement of the lower dorsal vertebrae. Involvement of the lumbar vertebrae was associated with painful hips and thighs as in disease of the hip joint and as in so-called meralgia paraesthetica or with pain over the back and lower extremities as in sciatica.

It becomes apparent from the widespread nature of the patient's complaints that involvement of various spinal roots may be associated with subjective sensory disturbances, seemingly due to visceral disease, and herein lies the importance of recognizing the radicular syndrome based on spinal osteo-arthritis.

## REGIONAL RADICULITIS CERVICAL RADICULITIS

Since arthritis of the spine as a cause of the radicular syndrome has received little attention, it is not at all surprising that root pain corresponding to the distribution of the first to third cervical roots over the head has been commonly included under the blanket term of "headache." These roots supply the back of the head from the occiput to the vertex and a small area over the mandible (figs 3 and 4F).

*Headache*—Irritation of the first three cervical roots manifests itself subjectively to the patient as "headache" over the occiput, the back of the head and the vertex. This type of headache has been commonly spoken of in the literature as "indurative or rheumatic head-

ache,' and has been thought to be due to fibrositis or fibromyositis of the fascia, which these nerves pierce in order to gain the periphery<sup>31</sup>

Hartenberg<sup>32</sup> commented on the association of indurative headache and arthritis of the cervical spine. Indurative or rheumatic headache has so many striking points of similarity with arthritis that Patrick<sup>33</sup> labeled it "arthritic headache." Holmes<sup>31</sup> showed that a pathologic process in the higher cervical vertebrae could be the cause of persistent headache and ascribed it to irritation of the spinal roots that furnish fibers to the occipital nerves. In his case, tuberculosis of the first cervical vertebra was considered the causative agent of irritation of the roots.

Patrick, in discussing indurative or rheumatic headache, gave an interesting review of the discovery, by Scandinavian masseurs, of tender nodules occurring in occipital, suboccipital and vertex headache. He pointed out the inaccuracy of palpation of the nodules by masseurs and others, whose anatomic and physiologic knowledge was not accurate, 'Nodules can be felt by anyone—and a masseur is especially apt to be feeling things—especially glands, subcutaneous fat, etc.' Patrick did not believe that palpable nodules had any connection with the disease. He cited Auerbach, who found a nodule the size of a nut in one patient who presented symptoms, and a similar "kernal" in another patient without symptoms and in conclusion pointed out the necessity for further investigation of localized lumps by "real pathologists, rather than by masseurs." In discussing indurative headache, Holmes<sup>31</sup> cited Muller who insisted that the palpable nodules were not the essential factors of the headache but that they were due to the higher tonus of the affected muscle which, on the other hand, was a result of latent arthritis in the adjacent joints. When a careful analysis of Patrick's description of indurative headache is made, the radicular distribution of the radiation of pain and the factors common to cervical radiculitis become striking. Symptoms, he stated, are brought on by stooping, straining coughing and generally, physical exertion.

In 1927, Holbrook<sup>34</sup> described a series of cases in which headache was the prevailing symptom. Hypertrophic osteo-arthritis of the upper cervical vertebrae was a constant observation.

In this series of thirty cases eight patients complained of headache. This group presented certain common symptoms, which were characteristic enough to enable one to recognize the syndrome quite

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31 Holmes, Gordon. Headaches of Organic Origin, *Practitioner* 90:968, 1913

32 Hartenberg, M., quoted by Patrick (footnote 33)

33 Patrick, H. T. Indurative or Rheumatic Headache, *J. A. M. A.* 71:82 (July 13) 1918

34 Holbrook, C. S. Headache Due to Arthritis of the Cervical Spine, *South M. J.* 20:225 (March) 1927

readily. These were pain dependent on movement of the neck, or on relaxation of the supporting structures of the cervical spine, as in sleep, and aggravation or induction of symptoms by Dejerine's sign (coughing, straining and sneezing)

Headache was described as a dull ache, or soreness and burning at the occiput on either side, or both sides, which "shot" most commonly to the vertex, and less frequently radiated from the occiput to the side of the head and temples. Headache was a symptom when the second or third cervical vertebrae, or both, were involved. In order of frequency, subjective sensations at the vertex were piercing pain, tenderness, soreness, burning or dull aching.

Symptoms were uniformly produced or aggravated by movement of the head. According to frequency, Dejerine's sign, sudden movement and raising the head on awakening were the most common aggravating factors. The patient awakened at night with this pain and found relief by a change of position. As previously pointed out, a hard bed was preferred, the patient obtaining greatest relief when lying flat on the back. The wearing of a splinting collar, heat, massage and stretching of the neck were measures which gave relief. On movement, audible crepitations in the neck were frequently noticed. Occasionally, tenderness at the occiput was observed. The symptoms tended to disappear after the patient had been up and around after rising, provided he did not move the neck suddenly.

The patient complained of "headache," without the likelihood that actual headache existed. The presenting symptomatology was that of pain and aching over the distribution of the first, second and third cervical roots over the back of the head, and was always found when the second or third cervical vertebra, or both, showed an osteo-arthritic process. Headache was not a solitary symptom, but was found in association with symptoms over the area "up and down the back of the neck." Symptoms over this area were associated with osteo-arthritis involving the fifth and sixth or seventh cervical vertebrae. Headache, per se, as a symptom was not present in patients who showed a localized lower cervical osteo-arthritis, unless the upper cervical vertebrae also showed evidence of pathologic changes.

Involvement of the cervical roots with symptoms of headache may also occur in other pathologic processes of the higher cervical vertebrae, as pointed out by Holmes<sup>35</sup>

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35 Holmes (footnote 31) Worthy of mention is one patient not included in this series, who presented symptoms over the distribution of the first, second and third cervical roots following an ankylosing process which involved the upper three cervical vertebrae. The x-ray picture interpreted by the roentgenologist read "An old destructive process probably the result of an infectious arthritis"

*Sore Neck and Painful Shoulders and Arms*—Discussions on spinal osteo-arthritis associated with cervical radiculitis have been reported chiefly in the French literature<sup>36</sup> as rheumatic diseases of the spine and as rheumatic radiculitis. In the older English literature, frequent references were made to the occurrence of brachial neuralgia and neuritis in "rheumatic and gouty people"<sup>37</sup>. Buckley<sup>38</sup> stated that, "apart from injury, gout is undoubtedly the most prominent etiological factor and in many cases the only discoverable cause, while in others it acts merely as a predisposing condition". Rheumatism and gout were apparently used by the earlier French and English writers in a general manner, indicating the group of deforming arthritic diseases, rather than being restricted solely to the disease associated with disturbances in uric acid metabolism.

Buckley also observed sensory alterations such as anesthesia and hyperesthesia. These changes were very slight, but often were present after other symptoms had disappeared. Other reports can be found, such as Distin's,<sup>39</sup> in which the clinical description strongly suggested the presence of spinal osteo-arthritis and associated involvement of the spinal roots. In this country, Bassoe,<sup>20</sup> Elliott<sup>28</sup> and Nielsen<sup>40</sup> associated cervical osteo-arthritis with radicular symptoms in neuritis of the shoulders.

Symptoms referable to the lower cervical roots were found in eighteen patients in this series. Thirteen of these described symptoms "up and down the back of the neck" and the side of the neck, with radiation over the shoulders and the outer side of the arms. One patient of this group complained of pain at the side and front of the neck, a diagnosis was made of adenomatous goiter with thyrotoxicosis, and the patient was referred to the University of California Hospital for thyroidectomy. Observation on the surgical service failed to confirm the diagnosis, and the patient was referred to the outpatient department for further study. Five patients complained solely of symptoms "up and down the back of the neck". Painful shoulders (fig 4D), or aching and soreness on the outer side of the neck, and pain, aching, soreness and stiffness "up and down the back of the neck" (fig 4C) were complained of when the fourth, fifth and sixth or seventh cervical vertebrae were involved. Pain radiating down the outer side of the arms, often to the base of the thumbs, was part of the picture, and occasionally paresthesia in the fingers in the form of tingling and numbness was

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36 Camus (footnote 4) Ler1 (footnote 5)

37 Simon, R. M. Brachial Neuralgia, Brit M J 2 71 (July 11) 1903

38 Buckley, C. W. Brachial Neuritis, Lancet 1 1042, 1904

39 Distin, H. A Note on Brachial Neuralgia, Brit M J 1 124, 1904

40 Nielsen, J. M. Radicular Syndrome, J A M A 88 1623 (May 21) 1927

present Over the outer side of the arm, the symptoms were described as pain, aching or heaviness When the fifth and sixth, or fifth to seventh cervical vertebrae alone were involved, the subjective complaints were often restricted to the area "up and down the back of the neck," between the cervical prominence and the occiput (fig 4C) If the shoulder, or the acromioclavicular joint, was also the seat of arthritic changes, crepitation in the shoulder was an added symptom

The cardinal symptoms were pain, aching and soreness, induced or aggravated by movement of the spinal vertebrae, associated most commonly with sneezing, straining at stool and coughing (Dejerine's sign) and raising the head on awakening Sneezing induced symptoms more often in the cervical spine than coughing or straining at the stool Other aggravating factors and symptoms have been described in detail, in the section on general symptomatology

Sensory tests with the cotton tuft, as previously outlined, were conducted on all patients of this group Sensory changes were, for the most part, bilateral in distribution Hyperesthesia could be found more often in the cervical region, in patients with symptoms of more than five years' duration, whereas, in other regions, hypesthesia was common Anesthesia to the cotton tuft was noted in the cervical region, when the symptoms were of more than five years' duration, but did not occur as frequently as elsewhere Flattening of the thenar and hypothenar eminences was noted in certain patients, but actual paralysis of these muscle groups could not be demonstrated

Physical examination usually showed restricted mobility of the cervical spine Motion induced crepitations over the back of the neck, which could be heard with the stethoscope, and sometimes these were palpable When arthritis of the shoulder joint was also present, crepitations could be elicited on movement of the shoulder joint

To the laity, the condition of painful shoulders is commonly known as neuritis, neuralgia and sore arms Because the pain is referred to this area, the shoulder joint receives considerable undeserved attention Even the thyroid is not immune from suspicion when pain is referred to the side and front of the neck Arthritis of the shoulder joint and osteo-arthritis of the cervical spine may exist together Errors in diagnosis can be avoided only by a careful study of each case, taking into consideration the nature and distribution of the symptoms, and the careful examination of the shoulder joint, as suggested by Patrick<sup>33</sup> Sensory alterations, of the nature described, cannot be explained by disease of the shoulder joint Involvement of the anterior cervical roots, resulting in confusion with the muscular atrophies of the upper extremity and shoulder girdle, has been reported<sup>40</sup>



## DORSAL RADICULITIS

*Heart Disease, Heart Neurosis, Pulmonary and Pleural Disease and Operations on the Breast*—In a paper on the importance of examination of the spine in the presence of thoracic and abdominal pain, Phillips<sup>41</sup> called attention to pain over the precordium simulating angina pectoris. He did not test for sensory disturbances. Kilgore,<sup>42</sup> reporting a large series of cases with precordial pain, noted that in the normal group a common type of precordial pain was related to certain movements of the left arm, position in bed, etc. To the normal group, he applied the term "psuedo angina pectoris." Although he did not ascribe the syndrome to spinal osteo-arthritis, he pointed out the character of the pain, which was different from that of true angina.

Heart disease occupies the attention of the patient when the second to the fifth dorsal vertebrae are involved, and the physician is apt to be misled by complaints of pain and aching over the precordium with radiation in an anginoid manner toward the shoulder and the armpits, down the inner side of the arm and often to the small finger (fig 4I). To a certain extent, in introspective persons, tachycardia and fear of breathing are concomitant sensations. Soreness and paresthesia, such as numbness and burning, are also symptoms. The physician recognizes the exaggerated apprehension of the patient, and the picture of the neurotic or the irritable heart, or, if the attack is severe, of angina pectoris is simulated.

Unlike the condition in patients with angina pectoris, however, the blood pressure of these patients is either within normal limits, or other outstanding evidences of vascular disease are absent. They get little relief from the usual symptomatic treatment, their complaints are persistent, they see many physicians and it is not unusual to find that they have been labeled as "neurotics," or classed under other "waste basket" terms. While the pain may radiate as in angina pectoris, the outstanding feature of this syndrome is the aggravation or onset of symptoms with movements of the spine, even when the patient is at rest, such as being awakened at night by pain, or onset of pain when sitting in a chair. The nocturnal pains are relieved by a change of position. The symptoms described in the paragraph on general symptomatology apply to this group also.

When the symptoms in the upper part of the chest are most severe on the right side and Dejerine's sign to coughing and sneezing is

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41 Phillips John. The Importance of Examination of the Spine in the Presence of Intrathoracic or Abdominal Pain, Proc Interstate Post Graduate Medical Association of North America, Kansas City 3 79 (Oct 17-21) 1927

42 Kilgore E S. Angina Pectoris and Pseudo-Angina. A Clinical Study with Especial Reference to Lancinating Pain, J A M A 87 455 (Aug 14) 1926

positive, the condition may be diagnosed as tuberculosis or pleurisy. If the patient is a woman in the cancer age, she and the physician focus considerable attention on the breasts, and operation for the removal of a "pea-sized" benign cyst may be the result.

Symptoms over the distribution of the upper five dorsal roots were found in ten patients. Of these, tuberculosis with pleurisy had been diagnosed in one, and pleurisy of the left side in another. In the former patient, at the time of onset, Dejerine's sign was positive to coughing and sneezing. The symptoms were greatest on the right and were confined to the area supplied by the second to fifth dorsal roots. These circumstances led to a diagnosis of tuberculosis with pleurisy. In the history, sufficient weight was not given to the fact that the pain was radicular in distribution, and movements of the spinal column, such as stooping and getting in and out of bed, were as prominent in the induction of symptoms as were coughing and sneezing. The laboratory work, necessary to confirm a diagnosis which was to alter this patient's mode of living, was not obtained. Four patients, including the one whose condition was diagnosed pleurisy of the left side, complained of heart trouble and were examined for cardiac disturbances (fig 5). Three had symptoms across the upper part of the back, between the shoulder blades. Two patients, who did not have complaints referred to this area, were found to have suffered from disturbances over the upper part of the chest and back in previous years. One of the latter patients has been included in those who complained of heart trouble. One patient in the cancer age had a benign cyst, the size of a pea, removed from the left breast. The surgeon remarked that the amount of pain and disability was not accounted for by the cyst. The same patient, at another examination, was said to be neurotic, because of the diffuseness of her symptoms.

*Gastric Disturbances and Diseases of the Gallbladder*—Osteoarthritic involvement of the sixth, seventh, eighth and ninth dorsal vertebrae was associated with pain, burning, tingling, heaviness, pressure and stabbing, and "gas" in the epigastrium, and the patient associated these symptoms with the digestive apparatus. For such conditions, it was not uncommon for patients to have consulted gastro-enterologists.

Involvement of the same roots, with manifestations greater on the right side, was revealed as pain or aching over the right upper quadrant with radiation along the ribs to the shoulder blade, or across the abdomen. This area, the topographic distribution of dorsal roots six to nine, is the same area over which pain from a diseased gallbladder is referred (fig 4G). Pain in this region must be differentiated from disease of the gallbladder. Osteo-arthritis of the spine with root pain may account, perhaps, for the large percentage of operations on the gallbladder that

fail to give relief Muller,<sup>43</sup> in a discussion of the noncalculus gallbladder, pointed out that from 30 to 40 per cent of patients still complain of symptoms after operation, and he urged against the diagnosis of disease of the gallbladder on threshold symptoms, and against operation in the absence of gross demonstrable lesions, as shown by cholecystography and other methods. The observations in this series indicate the necessity of a careful analysis of each case, and the presence of osteo-arthritis of the spine should be given due consideration in the absence of outstanding symptoms of disease of the gallbladder. Carnett,<sup>44</sup> in a discussion of the disease of the gallbladder simulated by intercostal neuralgia of the abdominal wall, also discussed the problem of the unsatisfactory end-results of operation on the gallbladder without calculus.

Disease of the gallbladder and radicular symptoms in spinal osteo-arthritis may coexist. The train of symptoms produced by each can be separated quite readily.

Fourteen patients presented symptoms over the distribution of the sixth to ninth dorsal roots, six patients complained of stomach trouble and pain in the left hypochondrium. Three of these had first visited gastro-enterologists. One history of the three disclosed a long list of therapeutic procedures, including surgery and a Sippy diet, all of which had been tried without success. Both the patient and the physician considered the symptomatology of gastro-intestinal origin. The history did not show any clearcut indication for the Sippy regimen, and our examination and laboratory procedures likewise directed attention away from the gastro-intestinal tract. Interestingly, another physician had prescribed an orthopedic belt for the patient, and it also had failed to furnish relief. Examination of the belt showed it to be of the "low-back" variety, designed for support of the lumbar spine. It was not long enough to furnish any sort of support to the mid-dorsal spine where support was most needed. This mistake indicates the necessity of the physician having a working knowledge of the distribution of nerve roots. To be effective, a belt for relief of radicular pain of the lumbar region should be large enough to support the mid-dorsal and lower dorsal regions of the spine.

Four patients presented symptoms over the distribution of referred pain of the gallbladder, and three were originally studied for disease of the gallbladder. One history of the three showed entries in the cardiac clinic for angina pectoris (precordial pain), in the gastro-intestinal

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43 Muller, G. P. The Noncalculus Gallbladder, *J. A. M. A.* **89** 786 (Sept. 3) 1927.

44 Carnett, J. B. The Simulation of Gallbladder Disease by Intercostal Neuralgia of the Abdominal Wall, *Ann. Surg.* **86** 747 (Nov.) 1927.

clinic for chronic cholecystitis (pain in the right upper quadrant) and in the surgical clinic for chronic appendicitis (pain in the right lower quadrant). The symptoms varied only in their location (fig 5). The fourth patient had a chronic fibrous cholecystitis, without stone, and radicular symptoms coexisting. Cholecystectomy failed to relieve the outstanding symptom, pain. Another patient, in whom exploratory laparotomy revealed a carcinoma of the gallbladder, presented symptoms of chronic cholecystitis, which were partially masked by the symptoms of an upper dorsal radiculitis with pain over the precordium and a mid-dorsal radiculitis with involvement of the same roots over which pain is referred from the gallbladder. Sensory alterations, consisting of hypesthesia to the cotton tuft were present. One case was diagnosed as pleurisy, of the right side, and one patient in addition complained of radicular headache. The past history of one patient who did not have any complaints referable to the mid-dorsal roots revealed an area of root distribution that had previously been troublesome.

*Pseudo-Appendicitis*—Discussions of extra-abdominal lesions as the cause of a syndrome simulating appendicitis have been presented by Carnett,<sup>45</sup> a surgeon, and by Phillips,<sup>41</sup> an internist. The former reviewed the literature of so-called pseudo-appendicitis, and ascribed the condition to intercostal neuralgia of the lower intercostal nerves. He discussed the methods of differentiating this condition from acute and chronic appendicitis.

Phillips called attention particularly to the osteo-arthritic spine as a cause of irritation of the lower dorsal roots. Symptoms were manifested peripherally as pain over the lower part of the abdomen, and included the region of the appendix.

Reference to figure 3 shows that the tenth to twelfth dorsal roots supply the area over the lower part of the abdomen between the umbilicus and inguinal ligaments, and posteriorly between a line drawn through the twelfth dorsal spine, above and the iliac crests, below. In this series, it was found that when the tenth to twelfth dorsal roots were affected, the appendix received considerable attention when the symptoms were greatest on the right, in women, the tubes and adnexa received attention when the symptoms were greatest on the left. Pain aching and stabbing (the latter usually in the right lower quadrant), which was referred to the small of the back, or began there and radiated forward across the abdomen, were the commonest complaints and were associated with osteoarthritic involvement of the tenth to twelfth dorsal vertebrae. As shown in the section on general symptomatology, symp-

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45 Carnett, J. B. Chronic Pseudo-Appendicitis Due to Intercostal Neuralgia, *Am J M Sc* **174** 579 (Nov.) 1927, Acute and Recurrent Pseudo-Appendicitis Due to Intercostal Neuralgia, *Ibid* **174** 883 (Dec.) 1927.

toms were induced by movement, as in walking, stooping and bending, and were associated with coughing, sneezing and straining, or came on at night when the patient slept. Relief was obtained by mechanical means, such as strapping the back. Sensory changes in this area were similar to those found in other regions.

Fifteen patients in this series had symptoms over the distribution of the tenth to twelfth dorsal roots, associated with osteo-arthritis of the adjacent vertebrae. Four of these complained chiefly of disturbances in the right lower quadrant, two had been operated on for appendicitis without relief of symptoms and a third had been urged to submit to an appendectomy (fig 5). The last patient still has her appendix. One of the two patients who had been operated on for chronic appendicitis showed an isolated osteo-arthritic involvement of the ninth, tenth and eleventh dorsal vertebrae. The outstanding symptom in the post-appendectomy cases and in the patient who refused to submit to the operation, was pain dependent on movement of the spine, or associated with coughing, straining and sneezing. The presence or absence of the appendix has not altered the situation at all, for each continued to suffer from pain. Four of eleven who complained of pain across the lower part of the abdomen, also complained of backache across the small of the back. Two had undergone operations on the pelvic organs, without relief of symptoms.

If the existence of pain referred from a distant point with origin in the spine is kept in mind in the differential diagnosis in conditions of the lower part of the abdomen, particularly in patients over the age of 35, the diagnosis of appendicitis based on minimal symptoms will not be made in the absence of the order of occurrence of symptoms, as stressed so strongly by the late John B. Murphy<sup>46</sup>. A history, carefully elicited, will bring out the relation of pain to movement, and to coughing, sneezing and straining, and other root areas not complained of at the time will be uncovered.

#### LUMBAR RADICULITIS

*Myalgia Paresthetica and Arthritis of the Hip Joint*—Pain, burning or aching starting over the upper part of the thigh at or behind the iliac crests, at the sides of the thigh with radiation into the inguinal ligament area or downward across the front of the thigh to the knee (fig 4J), were complained of by six patients who showed an osteo-arthritic process localized to the upper lumbar vertebrae. Rosenheck<sup>11</sup> and Bassoe<sup>20</sup> considered osteo-arthritis in this region of the spine a cause of so-called

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<sup>46</sup> Murphy, J. B., quoted by Cope in *The Early Diagnosis of the Acute Abdomen* ed 4, London: Oxford Medical Publications, 1927, p. 62.

meralgia paresthetica Stookey<sup>47</sup> did not consider Rosenheck's cases as true meralgia paraesthetica, because of the radicular nature of their disturbances. When symptoms are confined to the upper part of the thigh, the pain, as in the region of the shoulder, is often ascribed to arthritis of the adjacent joint. In this series, the fabere<sup>48</sup> sign, as suggested by Patrick,<sup>33</sup> was noted. Cases were not included in this group unless the symptoms and sensory changes were purely radicular in distribution.

#### REPORT OF CASE

P. A., a housewife, aged 40, had suffered at various times during the past ten years from pain up and down the spine, pain, soreness or burning, which radiated from the small of the back to the lower part of the abdomen, pain up and down the back of the neck, and occipital "headache" which sometimes radiated to the top of the head. Movement, such as getting in and out of bed, induced or aggravated symptoms. Fourteen months before examination an appendectomy was performed, because of the pain in the lower part of the abdomen. The symptoms were not relieved.

The symptoms of her present illness were pain, soreness and burning, beginning at the iliac crests, more severe on the right and radiating down the outer side of the thigh over the distribution of the lateral femoral cutaneous nerve of the thigh. On questioning, it was found that radiation also extended across the front and the inner side of the thigh to the knee. The total area of subjective disturbances covered the distribution of the first to the third lumbar roots (fig. 4J), which was made up of four peripheral nerves: the lateral femoral cutaneous, the anterior femoral cutaneous, the lumbo-inguinal and the ilio-inguinal nerves of the thigh. Symptoms were worse during the night, and were induced or increased by straining at stool, sitting in one position any length of time or attempting to rise from a chair.

Physical examination revealed two operative scars, one in the midline and one over the McBurney area. Marked tenderness to pressure was present below the anterior iliac spines. Examination of the back showed moderate restriction of mobility of the lower part of the dorsal spine. Sensory examination with the cotton tuft revealed hypesthesia over the back of the neck, and between the upper parts of the shoulder blades, corresponding to the fifth to the seventh cervical roots, hypesthesia over the small of the back between the twelfth dorsal spine and the sacrum, corresponding to the ninth to twelfth dorsal roots, and over the upper sides of the thigh, the front and inner sides corresponding to the first three lumbar roots. The fabere sign was not elicited. Gastro-intestinal consultation, including a gastro-intestinal series, genito-urinary consultation and cystoscopy and gynecologic consultation failed to uncover pathologic changes that would explain her symptoms. The consultants felt that the source of the trouble was outside the abdomen. The Wassermann reaction of the blood and the results of a Kahn test were negative. X-ray examination of the spine showed osteo-arthritic changes about the first, second, sixth and seventh cervical vertebrae, the sixth dorsal vertebra, the ninth to twelfth dorsal vertebrae and the first lumbar vertebra.

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47 Stookey, Byron. *Meralgia Paraesthetica. Etiology and Surgical Treatment*, J. A. M. A. 90.1705 (May 26) 1928.

48 The word "fabere" was introduced by Patrick to describe the movements of the thigh, in performing the maneuvers of this test, namely, flexion, abduction, external rotation and extension.

*Comment*—In the history of the chief complaint, the patient presented symptoms of pain and paresthesias over the distribution of the lateral femoral cutaneous nerve of the thigh (old term, external cutaneous) Objective sensory disturbances were present in this area Had the patient not been questioned regarding the total radiation of the subjective disturbances, the radicular nature of the symptoms would not have been clear Confining oneself to the chief complaint, pain and paresthesias along the lateral aspect of the thigh, this case might have passed for one of meralgia paraesthetica Disturbances in this patient, however, were bilateral (fig 4J), and symptoms were dependent on movement of the spine and Dejerine's sign While meralgia paraesthetica by definition is a syndrome affecting a peripheral nerve, namely, the external cutaneous nerve of the thigh, it is readily seen that the radicular nature of the osteo-arthritic syndrome affecting the roots of origin of this nerve might easily be overlooked Rosenheck<sup>14</sup> particularly pointed out that the condition known by definition as meralgia paraesthetica has not been separated from the painful paresthesias of the thigh of radicular distribution, due to spinal osteo-arthritis

*Sciatica*—Localized pain over the sacrum and often present in conjunction with pain on the inner sides of the legs (fig 4B), or pain over the sacrum radiating downward over the anatomic distribution of the first and second sacral spinal roots (fig 4A), was found when an osteo-arthritic process was present anywhere below the level of the third lumbar vertebra A similar condition and distribution also were found when a sacralized transverse process of the fifth lumbar vertebra or disease of the sacro-iliac joint was present Distribution of pain over the first and second sacral roots is commonly called sciatica and includes the cutaneous distribution of the posterior cutaneous nerve of the thigh and the peroneal division of the sciatic nerve Paresthesia, such as numbness and tingling over the posterior surface of the thigh and over the dorsum of the foot, were occasionally symptoms

The radicular nature of sciatica, with its subjective and objective sensory disturbances, has been recognized by orthopedists and has been amply described by Danforth and Wilson,<sup>13</sup> and by others Our patients showed objective sensory alterations as tested with the cotton tuft and subjective disturbances dependent on motion, such as walking, bending and lifting and on straining, coughing and sneezing

Symptoms over the roots, which are commonly involved in so-called sciatica, were present in twenty-three patients Backache (localized pain over the sacrum) was the outstanding symptom Sciatic radiation occurred in sixteen patients Backache, concomitant with pain on the inner sides of the legs was present in seven One patient demonstrated sensory changes over the root distribution of sciatica at a time when

active symptoms were absent. Spinal osteo-arthritis coexisted with disease of the peripheral joints. The two conditions were also associated in four other patients. Symptoms were first noted thirty-five years before examination, and they were quiescent except in the region of the gallbladder. The history, however, was abundant in its information of the onset, progressive involvement of various spinal roots and session of symptoms in the various root areas during the many years. Bilateral sensory disturbances were demonstrable with the cotton tuft.

The most marked sensory disturbances of the entire series were found in a patient who complained of sciatica. Osteo-arthritic changes in the lower lumbar vertebrae and a left unilateral sacralized transverse process of the fifth lumbar vertebrae coexisted. Complete anesthesia to pain over the fifth lumbar and first sacral roots, and hypesthesia to the pin over the second sacral root was present on the same side.

Tender points along the sciatic nerve were not found. The Lasègue sign was inconstantly elicited and when present was extremely mild.

#### SUMMARY

Radiculitis may be defined as a symptom-complex manifested by alterations of sensation or of changed motor function, which show by their distribution that the disease is in the spinal root. The radicular syndrome in hypertrophic osteo-arthritis of the spine, as seen in this study, consisted of restricted mobility of the spine, root pains and root sensory alterations, produced or aggravated by movement, and associated with Dejerine's sign.

In the history of the chief complaint, it is commonly found that the patient outlines the cutaneous distribution of the root or roots involved with anatomic accuracy. In the past history, however, areas which were troublesome at some previous date, but were symptomless at the time, are not always outlined with the same degree of accuracy. The past history then becomes extremely important. If it is gone into carefully, previous symptom-bearing areas will be accurately outlined by the patient. In either event, it is important to determine the limits of each painful area and the extent of radiation of symptoms, because, in certain regions of the body, roots that are widely separated in the cord supply adjacent cutaneous areas. (The areas bordering the heavy lines in figure 3 should be noted.) If this procedure is adopted, the past history of even the apparently silent case will yield a story of chronological progression or regression and quiescence of the disease, and symptoms that indicate the involvement of various spinal nerve roots over a period of years. The charting of such cutaneous areas of nerve root distribution and a listing of the roots involved will enable one to anticipate the extent of the x-ray evidence of the osteo-arthritic process.



Pain at night which awakens the patient and necessitates a change of position for relief, is a common symptom. Although the patient complains of one side more than the other, bilateral symptomatology is the rule, the right side receiving more attention over the abdomen, and the left side over the upper part of the chest and the precordium. Questioning is sometimes necessary to bring out the bilateral nature of symptoms. Characteristic of this syndrome is the root distribution of the symptoms. Measures which afford symptomatic relief are lying flat on the back or on a preferred side, a hard mattress, the placing of boards under the mattress, the wearing of a corset or other mechanical means of immobilizing adequately the affected vertebrae and physiotherapy such as baking, heat and massage.

The outstanding symptom of this syndrome is pain. It is variously described according to the patient's mode of expression. Symptoms are dependent on three factors: (1) movement of the spinal column, (2) relaxation of the supporting musculatures of the spinal vertebrae and (3) mechanical factors which increase intraspinal pressure, such as coughing, sneezing and straining as at the stool. These three acts are grouped together under the name of Dejerine's sign.

Under the heading of movement, typical phrases were encountered such as rising after having been in a sitting position, raising the head on awakening, getting out of bed, walking, sitting in one place for any length of time, a change of position while sitting or lying, stooping, straightening after having been bent over, inability to sit up in bed from the supine position and the necessity of rolling out of bed on one side or the other. Under this category may also be included the reproduction of symptoms occurring during the various movements to which the spinal column is subjected when it is being tested for mobility. The mechanism involved under 'relaxation of the supporting musculatures of the spinal vertebrae' explains the occurrence at night of symptoms which awaken the patient from sleep, the necessity of a change of position at night to obtain relief from pain, the preference for a hard bed and the relief obtained by placing boards under the mattress. The presence of the third factor, Dejerine's sign, is a useful sign in root-zone disease. This has been indicated by Dejerine<sup>17</sup> and by Mayer.<sup>22</sup> Dejerine's sign also occurs in other forms of disease of the spinal roots and does not give a clue to the etiologic factor. The presence of crackling in the neck, shoulders, hips or knees during movement, Heberden's nodes and x-ray evidence of spinal osteo-arthritis, when associated with Dejerine's sign, furnish presumptive evidence of the osteo-arthritic etiology.

The sensory examination requires great care and patience. One or two areas were selected at a given examination, usually the area

of the chief complaint. Other areas were left for examination at another time. The selected area was tested once, the outlines of the involved area were recorded and no other sensory examination was made at that visit. This procedure was adopted because of the ease with which patients fatigue to the examination of light touch, and the confusion of results obtained when examination was continued after fatigue had set in.

Bilateral sensory changes were found, which consisted most commonly of hyperesthesia, hypesthesia or anesthesia to the cotton tuft. Marked hypesthesia or anesthesia with the cotton tuft was associated with slight hypesthesia to the pinpoint. Hyperesthesia to the cotton tuft was commonly present when the onset of symptoms dated within one year, or when an exacerbation of symptoms occurred in a given area within a year. Hypesthesia and anesthesia to the cotton tuft were common in patients whose symptoms extended beyond a five year period. In the area over the back of the neck, side of the neck and shoulders, the time relations were not so constant, hyperesthesia being more common than in other regions, even in patients with symptoms of many years' duration.

In patients with a long standing, diffuse, osteo-arthritic involvement of the spine, sensory changes were difficult to demonstrate, unless the hypesthesia was marked, or unless anesthesia to the cotton tuft was present. Such patients seemed to have a dulled sensorium to light touch over most of the body, and slight changes to light touch could not be demonstrated satisfactorily because of the lack of an unaffected area, other than the face, to use as a standard for comparison.

The physical examination revealed restricted mobility of the spine, varying from the involvement of a few vertebrae to the poker-like rigidity of the entire spine, which was seen in one patient. The vertebrae affected corresponded consistently to the origin of the roots involved, as determined in the history and in the sensory examination. The history and sensory examination, in turn, enabled one to anticipate accurately the pathologic process shown by the x-ray examination. Laboratory procedures, including the Wassermann test of the blood, gave normal values, or were negative. The results of the Wassermann test on the spinal fluid and the colloidal gold test, done on four patients, were negative.

An analysis of thirty cases of hypertrophic osteo-arthritis has been presented. Cervical radiculitis was found in twenty-six patients. Headache was a symptom in eight patients with cervical radiculitis, and was associated with osteo-arthritic changes in the second and third cervical vertebrae. Cervical radiculitis, with symptoms "up and down the back of the neck," was found in five patients who showed a pathologic

process in the fifth and sixth or seventh cervical vertebrae. Thirteen patients described symptoms "up and down the back of the neck," with radiation over the sides of the neck, shoulders and outer side of the arms. This group was associated with an osteo-arthritic process in the fourth, fifth and sixth or seventh cervical vertebrae. A mistaken diagnosis of thyroid disease was made in one patient.

Dorsal radiculitis, with symptoms over the distribution of the upper five dorsal roots, was found in ten patients. Diagnoses had been made of tuberculosis with pleurisy, pleurisy of the left side, angina pectoris, heart disease and cardiac neurosis. One patient had a benign cyst the size of a pea removed from the left breast, without relief of symptoms.

Fourteen patients presented symptoms of a dorsal radiculitis over the distribution of the sixth to ninth dorsal roots. Six of these complained of stomach trouble, and three had first consulted gastro-entereologists. Four patients presented pain simulating disease of the gallbladder. Of these, one had a chronic fibrous cholecystitis without stone, and was not relieved by operation, and in one patient who had a carcinoma of the gallbladder, the visceral symptoms were partially masked by the radicular pain. One case was diagnosed pleurisy of the right side. Two patients, who complained of backache across the region of the lower part of the chest, were also found to have had symptoms from the same roots over the area of the gallbladder at an earlier date.

Dorsal radiculitis with symptoms over the distribution of the tenth to twelfth dorsal roots was found in fifteen patients. Four complained chiefly of the right lower quadrant and required a differential diagnosis from chronic appendicitis. Two had been operated on for appendicitis without relief, and one had been urged to submit to an appendectomy. There was little difference in the symptoms of two patients who had submitted to appendectomy and the one who had been urged to do so and had refused. The outstanding symptom in each instance was pain. Of eleven patients who complained of bilateral pain across the lower part of the abdomen, four complained of backache across the small of the back, and two had undergone operations on the pelvic organs without relief of symptoms.

Six patients presented symptoms of a lumbar radiculitis over the distribution of the first three lumbar roots, simulating so-called meralgia paraesthetica.

Lumbar radiculitis, with symptoms over the distribution of the fourth and fifth lumbar roots, and the first two sacral roots, was found in twenty-three patients. The symptoms of this group are commonly included under the diagnosis of sciatica. Sixteen patients of this group complained of backache (pain localized over the sacrum) with sciatic

radiation, and seven complained of backache (pain localized over the sacrum) associated with pain on the inner side of the legs

The severe upper dorsal bowing, postural deformities, neck weakness and muscle atrophies, described by von Bechterew,<sup>1</sup> Strumpell<sup>2</sup> and Marie,<sup>3</sup> were not observed in our patients. This study concerned, for the most part, the patient whose vertebral changes were not marked

Hypertrophic changes in the knee, hip, shoulder or acromioclavicular joints were present in five patients. Subjective and objective sensory disturbances were present in these patients, and did not differ in any way from the disturbances observed when the process was confined to the spinal column. In one case of "poker spine" and involvement of the peripheral joints, active neurologic symptoms were minimal. The past history, however, revealed symptoms indicating a progressive involvement of various spinal nerve roots, with a subsequent quiescence during a period of thirty-five years. Bilateral sensory changes could be demonstrated with the cotton tuft. The x-ray examination revealed a mixed process consisting of the ordinary spur formations, atrophy of the bodies of the vertebrae, and calcification of the anterior ligaments.

Pain in the spinal column, localized to several vertebrae, as elicited by heavy percussion in Pott's disease and in new growths of the cord and vertebrae, was not found in this study. The root pain seen in this series was in no instance as severe as that seen in the former two conditions, and it lacked the spontaneity of the pain seen in tumors of the cord and vertebrae. Although symptoms interfered with sleep, in no case did the patient find relief by walking the floor or sleeping in a chair, as occurs in patients with new growths of the vertebrae and spinal cord. This fact was stressed by Parker and Adson.<sup>12</sup> Such maneuvers invariably aggravated the symptoms in our patients. The skin, overlying the spinous processes, was sometimes tender when the spinal roots to that particular cutaneous area were involved. Root symptoms and radicular sensory alterations were constantly associated with osteo-arthritic changes in the adjacent vertebrae.

#### DIAGNOSIS

The diagnosis of the radicular syndrome associated with spinal osteo-arthritis resolves itself into a careful history-analysis in which the symptom-bearing areas have been accurately determined, and their distribution compared with that of the spinal roots and the peripheral nerves. The radicular syndrome is characterized by distribution of symptoms according to spinal roots. The sensory alterations are also distributed according to the topography of the spinal roots. Bilateral sensory changes can be demonstrated with the cotton tuft. The presence of such changes, corresponding to the spinal vertebrae involved, is

diagnostic The demonstration of alterations in the sensation of light touch, however, is not essential to the diagnosis The outstanding characteristic of this syndrome is the relation of root symptoms to movement of the spinal column, their association with Dejerine's sign and the presence of hypertrophic osteo-arthritic changes in the adjacent vertebrae, which enter into the formation of the foramina of exit of the involved roots

In the history of the chief complaint, the distribution of a root or group of roots is usually demonstrated accurately These symptoms are most often the ones confused with the pain of visceral disease The occurrence of bilateral pain, which may be greater on one side, over areas corresponding to the topography of the spinal roots, produced or aggravated by movement of the spine, as described, and associated with coughing, sneezing or straining, indicates the presence of a radiculitis Root symptoms occurring during the day, induced by movement or protracted sitting, pain at night, which interrupts sleep and is relieved by a change of position, and a return of symptoms on awakening as the head is raised from the pillow is a characteristic and diagnostic train of circumstances When one or more of these are found in the history of the chief complaint, or in other similar symptom-bearing areas, a tentative impression of radiculitis should be entertained The induction or aggravation of root symptoms by one of the triad of coughing, sneezing or straining makes the presence of the radicular syndrome a certainty The association with clinical evidence of an osteo-arthritic process furnishes presumptive evidence of the complete syndrome Diagnostic aids of lesser value are the symptomatic relief obtained by strapping, the wearing of a supporting corset and physiotherapeutic measures, such as massage and heat

In the differential diagnosis of simulated visceral disease, the history is most important In the radicular syndrome associated with spinal osteo-arthritis, the history discloses other symptom-bearing areas with symptoms similar to those of the chief complaint The distribution of symptoms is sometimes most diffuse, but is always characterized by a radicular topography The physical examination shows varying grades of restriction of mobility in the spine, and these indicate the vertebrae which form the intervertebral foramina of the involved roots The cutaneous areas of the roots, as determined in the history, should correspond to those regions of the spinal column showing impaired mobility For example, symptoms over the lower part of the abdomen between the umbilicus and the inguinal ligaments are due to involvement of the tenth to the twelfth dorsal roots Over the back, these roots supply the cutaneous area directly overlying the spinous processes of the lumbar vertebrae The restriction in mobility should be present in the lower

part of the dorsal spinal column, since these roots emerge from the foramina between the ninth dorsal and the first lumbar vertebrae. The data of the involved roots, obtained from the history, and the restricted mobility of the spinal column, found in the physical examination, enable one to anticipate with considerable accuracy the vertebral involvement that the x-ray examination will show.

When properly done, the sensory examination with the cotton tuft will reveal alterations in sensation of a radicular nature, corresponding to the areas of subjective sensory disturbances and to the levels of the vertebral pathologic changes.

The presence of a radiculitis having been established, in the absence of syphilis, the history of diffuse root symptoms dependent on movement and associated with coughing, sneezing or straining, the diffuse sensory changes to light touch, the impaired mobility of the spine, the absence of local vertebral tenderness, the presence of cracking in the neck and other joints, the presence of Heberden's nodes and x-ray evidence of an osteo-arthritis process in the vertebrae adjacent to the involved roots establish the radicular syndrome in hypertrophic osteo-arthritis of the spine. The x-ray examination also aids in ruling out metastatic vertebral carcinoma and other destructive processes of the vertebrae and cord.

#### COMMENT

Hypertrophic osteo-arthritis of the spine is a common disease. It is conceivable that symptoms attending involvement of the nerve roots may be present as the sole cause of disability in the absence of visceral disease, or may coexist with visceral disease. It is not unusual to find that the radicular pain of hypertrophic spinal osteo-arthritis will bring a patient into the hospital as the chief apparent cause of disability, when a serious but less outspoken chronic visceral disease is also present, but masked by the striking symptoms of the former. On the other hand, this syndrome may simulate visceral disease and, as seen in this study, it becomes a likely explanation of the unsatisfactory results sometimes obtained in operations. Our analyses indicate that in adults over the age of 35, in whom pain is an outstanding symptom, a careful analysis of symptoms is necessary. Especially important is such an analysis when exploratory operative procedures are contemplated for the relief of vague abdominal conditions. When impaired mobility of the spine is present in regions which correspond to the cutaneous area of symptoms according to spinal roots, the radicular syndrome should be considered as an explanation of symptoms. If the radicular syndrome is present, it should be accorded a proper place in the disease picture, since it may simulate many visceral diseases, and in turn may mask the presence of visceral disease which may not be as outspoken in its symptomatology.

## CONCLUSIONS

1 Hypertrophic osteo-arthritis of the spine, root pain and radicular sensory alterations are definitely to be associated as a clinical syndrome

2 The symptoms of the syndrome are dependent on movement of the spine, relaxation of the supporting spinal musculature or coughing, sneezing and straining

3 The syndrome is characteristic enough to permit clinical recognition

4 The symptoms of the syndrome are independent of the visceral diseases which they simulate, and can be differentiated from the visceral diseases with which they may coexist

# THE CARDIOVASCULAR PROBLEM IN PNEUMONIA<sup>\*</sup>

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It has been repeated so often that death from pneumonia is the result of heart failure that this view seems to be accepted generally by the medical profession<sup>1</sup> The frequent observation of a dilated right side of the heart, with more or less evidence of toxic myocarditis at autopsy seems to be the basis for this assumption If it is true that the patient with pneumonia dies only because the heart muscle gives way, the clinical data observed during life should corroborate this fact If it is not true, it is important, from the standpoint of both therapy and prognosis, that the true pathologic physiology of the disease should be understood

The terminal dilatation of the heart is commonly believed to result from the combined effect of two factors (a) the impairment of functional integrity through the injurious action of the toxins of the infection on the muscle tissue of the heart, and (b) the increased cardiac load resulting from obstruction to the pulmonary circulation, due to the presence of the inflammatory exudate in the lung tissue

There can be no question that these factors exist That they are the factors of primary importance in the clinical picture is open to doubt

On the assumption that failure of the heart muscle is fundamental in mortality from pneumonia, there has grown up a therapy that is widely practiced in the United States, namely, the routine administration of digitalis<sup>2</sup> This practice has become much more general since the World War From my experience and from the observation of the work of my colleagues, I have formed an opinion that is at variance with the one commonly accepted This opinion is that the routine treatment with digitalis for pneumonia is ineffective, that not infrequently it is injurious, and that it is based on a failure to apprehend important factors in the pathologic physiology of the disease

Before presenting the data on which my views rest, it is proper to state that in the District of Columbia and the nearby regions the bacterial agent found in the majority of cases of pneumonia has been *Streptococcus hemolyticus* or *viridans*, or the two combined, rather than any of the pneumococci This has been true since 1916, at which time I began to have cultures of sputum made in my cases as a routine pro-

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<sup>\*</sup> Submitted for publication, July 15, 1928

1 Billings, F T Am J M Sc **171** 872 (June) 1926

2 Burrage, W S, and White, P D Am J M Sc **174** 260 (Aug) 1927



cedure Other local clinicians are finding out the same thing The idea is rather prevalent that lobar pneumonia is pneumococcus pneumonia, for it is assumed without making a culture of the sputum that if inflammation of the lung is primary and has a lobar distribution, it is of pneumococcic origin

Such is not the case Pneumonia of abrupt onset occurs which has a typical lobar distribution, so far as physical examination can determine, in which cultures from the sputum do not show pneumococci but streptococci The presence of pneumococci has been assumed merely on the basis of the examination of a stained smear of the sputum The method followed in the laboratory of the George Washington University consists in the selection of a specimen of the first sputum coughed up from the lungs, which usually contains blood, cultivation and subcultivation on different mediums, with inspection of the resulting colonies, further differentiation by tests of bile solubility, inulin fermentation, agglutination reactions and mouse pathogenicity Under this scrutiny it is found that not a few organisms which from the morphology seen in the smears appear to be pneumococci are streptococci Conditions are different farther north In a series of 2,000 cases, Cecil,<sup>3</sup> of New York, found that 95.6 per cent were due to the pneumococcus and 3.8 per cent to the streptococcus

#### REVIEW OF 100 CASES

A review of 100 cases occurring in the George Washington University Hospital has been made The cases are consecutive, with the exception of the omission of those cases in which complicating and terminal pneumonia was present, those in which there was a possible doubt of the correctness of the diagnosis and those in which the record was not sufficiently complete for the purposes of the study

This hospital is, so far as its private rooms are concerned, an open hospital, and about half the cases reviewed occurred in the practice of a relatively large number of physicians not connected with the hospital staff The data afforded, therefore, do not furnish a basis for a thorough clinical study They represent, however, a considerable variety of therapeutic procedure, the investigation of which was the primary object of the review The result shows that the aphorism of Loomis, uttered more than forty years ago, is as true today as it was then, namely, that there are some patients with pneumonia whom one cannot cure, some whom one cannot kill, and a certain proportion whom wise treatment and good nursing will help to recover

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3 Cecil, R. L. *Tr. Assoc. Am. Physicians* 41:208, 1926. Cecil, R. L., Baldwin, H. S., and Larsen, N. P. *Lobar Pneumonia*, *Arch. Int. Med.* 40:257 (Sept.) 1927. Cecil, R. L. *The Specific Treatment of Lobar Pneumonia*, *Arch. Int. Med.* 41:322 (March) 1928.

Digitalis was prescribed for thirty patients of this series as soon as the disease was recognized as pneumonia. In this group there were seven deaths, a mortality rate of 23.3 per cent (table 1). For few patients was the dosage sufficient to produce a full digitalis effect. Often it seems to have been given because it was considered the proper thing to do rather than because there was any clear idea of what was to be accomplished.

In thirty-four cases, the use of digitalis was instituted later in the course of the disease. In this group there were eight deaths, a mortality of 23.53 per cent (table 2). It is manifest that these figures do not furnish a proper basis for the comparison of the merits of early and later institution of treatment with digitalis. The physician who from the beginning of the disease uses digitalis therapy as a routine measure will use this treatment for many patients who would recover without the drug. The physician who does not use digitalis until the condition of the heart seems to demand it will employ it only in the graver cases. Not infrequently the drug is prescribed at the instance of a consultant who is not called in until the patient has begun to get worse.

In thirty-six cases digitalis therapy was not used, four deaths occurred, a mortality rate of 11.1 per cent (table 3). This group included a large majority of the mild cases, and no statistical value can be attached to the therapeutic results. Details of the cases reviewed are presented in the accompanying tables and charts.

It is apparent, therefore, that statistics on drug therapy that do not take into consideration all the factors presented by the individual patients cannot be relied on. It has always been recognized that advanced age tends to make the prognosis in pneumonia unfavorable. Other unfavorable factors are pronounced hypertension and obesity. The presence of some other chronic disease and especially the early and complete cooperation of the patient are individual factors of importance. Again, there is such a variation in the severity of individual cases that the statistical method of study presents too many sources of error to be trustworthy. I believe that progress in the understanding and management of this disease is made through careful observation and records by competent students of the clinical and laboratory phenomena.

My observations have led me to believe that the primary toxic effect on the circulatory system is exerted on peripheral blood vessels through the vasomotor system, and that failure of the myocardium is secondary or terminal. This view is based on the early depressant effect of the infection on the blood pressure, which depression runs parallel with the increasing gravity of the prognosis, and on the utter failure of digitalis to control the rate of the heart even when the drug is given in full dosage from the beginning. Furthermore, death from pneumonia may occur as a result of respiratory paralysis without myocardial failure. The

ordinary course of the fatal case is as follows For several days the pulse is of a fairly good quality and the blood pressure relatively constant, though the latter is reduced below normal, then, often abruptly, the pulse increases in rate, becomes weak and sometimes irregular, and loses the tone which it has hitherto maintained The blood pressure at that time shows a marked fall, the diastolic often more proportionally than the systolic The cardiac impulse becomes diffuse, and the quality of the heart tone is impaired Unless therapeutic measures are successful in restoring circulatory balance, death ordinarily ensues in twelve hours, or even less Autopsy shows the heart dilated, but histologic study does not show such deterioration of the heart muscle as toxic failure of the heart would lead one to expect, for example, as that seen in heart failure in cases of diphtheria

A more reasonable explanation of the circulatory failure occurring in pneumonia would appear to be as follows

- 1 There is an oxygen hunger of the tissues due to an elevation of the level of conversion of carbondioxide-hemoglobin into oxy-hemoglobin, probably an alteration in the blood, which is the essential physiologic defect caused by the disease

- 2 The increased respiratory rate and increased functional demand on the heart for oxygenated blood result in an accelerated and exaggerated heart action

- 3 The lowered blood pressure places an additional tax on the heart in its effort to carry on circulation without an adequate peripheral tone to support it

- 4 The right side of the heart is further incommoded by the resistance to the pulmonary circulation offered by the presence of the exudate in the lung

- 5 Last, but perhaps not least, the heart muscle itself does not get properly oxygenated blood for its adequate nutrition

The therapeutic need of the overtaxed heart, if one is to conserve its integrity, is not for something to increase the amount of work it is doing, as it is already working harder than it should, but rather for treatment directed toward lessening the functional load If digitalis were effective in slowing the rate of the heart in pneumonia, one should have a logical reason for its employment, that is, lengthening the rest period but I have never found that it does this It increases the contractile effort of the ventricular muscle, thus tending to use up its reserve more rapidly I consider that the indication for digitalis therapy in pneumonia is the same as in other conditions, namely, when failure of the heart muscle begins When this occasion arises, if considerable doses of the drug have been given over several days, one dares not use the large doses required to meet this emergency for fear of exceeding the limit of tolerance

On the basis of present knowledge, specific immunizing therapy is applicable only to a limited number of cases of pulmonary inflammation (pneumococcus type I). It seems that there is a prospect that a practical technic for the specific treatment of conditions due to types II and III will be provided<sup>4</sup>. Up to the present time, however, conspicuous and consistent failure has attended efforts to provide a successful specific therapy for streptococcic infections. It seems, therefore, that work will have to be continued along the line of conserving the vital forces in these cases until the activity of the infection has spent itself.

The therapeutic indications presented by the circulation in pneumonia are (1) to lower the toxemia, with a view to restoring the oxygen carrying capacity of the blood, (2) to increase the conversion of carbondioxide-hemoglobin into oxyhemoglobin, and (3) to sustain the blood pressure, thus relieving the heart as far as possible from the increased labor entailed by the effort to carry on the circulation unsupported by an adequate peripheral resistance.

I believe that helplessness in severe cases of pneumonia arises largely from one's inability to influence in any dependable way the pathologic elevation of the oxyhemoglobin threshold, which interferes with the necessary interchange of oxygen in the lungs. It is not known what causes this—whether it is an alteration in the red cell itself, in the blood serum or in both. The acid concentration theory, advanced by some investigators, if correct, should have led to a ready control of the situation through alkaline therapy. But there is some factor present that cannot be explained by the theory of quantitative alterations in the hydrogen ion concentration or in the alkali reserve. Nevertheless, a rather large experience in the use of the citrates and acetates of sodium and potassium in streptococcic infections of the respiratory tract has given me the impression that when administered early they have some effect in modifying the intensity of the infectious process and in lessening the frequency of extensions and complications to an extent not accomplished by other diuretics. There is urgent clinical need of research in the laboratories of biophysics and biochemistry in order to determine just what are the essential factors in pneumonia that cause the failure of the blood to take oxygen from the air in a normal fashion.

It is here that blood-letting seems to offer its most useful rôle. I believe that it accomplishes more than a mere mechanical relief of the load on the right side of the heart. I have not found that the best results from phlebotomy are obtained when its use is deferred till the heart shows signs of failure, though even then it is sometimes found to be a life-saving measure. In acutely toxic cases early phlebotomy has

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4 Cecil (footnote 3, third reference)

immediately improved the clinical picture, subjective and objective, and patients have gone on to recovery without causing further serious anxiety. If the blood-letting is deferred until the blood pressure has collapsed, benefit is not derived from it. The effect on the toxic state has seemed to be analogous to that which I have observed in venesection in sunstroke. Subjectively, the patient becomes more comfortable almost immediately. The respiration becomes more regular and is conducted with less effort and distress. I have had an exhausted patient go to sleep while the blood was flowing. Shortly after the flow begins, the pulse is felt to have undergone an alteration, becoming fuller, softer and losing its tense, thready quality. The systolic blood pressure does not show a marked change, sometimes falling from 5 to 10 mm, sometimes remaining stationary. In one case complicated by mitral stenosis I noted a rise of 10 mm during the flow of blood. The diastolic blood pressure, if lower than normal, often shows a tendency to rise during the venesection, with a further rise later.

I do not believe that phlebotomy should be undertaken in pneumonia with the idea that a definite amount of blood must be withdrawn at one time. Ordinarily, I take from 300 to 600 cc from an adult. The pulse is the guide which tells one when to stop. As the blood flows, the full wave, previously described as being established soon after the procedure is begun, is abruptly interrupted by a weakened subtonic wave. At this point the tourniquet should be loosened and the blood-letting stopped.

In certain cases, the inhalation of oxygen seems to be effective in keeping the anoxemia within the limits of tolerance. Occasionally, I see a patient in whom the relief obtained is almost dramatic. In other cases, continuous or intermittent inhalation of oxygen over a long period appears to enable cyanotic patients to hang on till the disease has spent itself. More frequently, however, this treatment has failed to change the clinical picture materially, no matter how high the concentration of oxygen. The blood defect that I have spoken of appears to reach such a degree that carbon dioxide conversion cannot be carried on, no matter how high the concentration of oxygen. I have never had access to an oxygen chamber, so I have had no experience with this method of administration of the gas.<sup>5</sup>

Working on the hypothesis that the circulatory failure occurring in pneumonia is primarily peripheral, and that the myocardial failure is secondary, I have recently made some observations on the behavior of patients in cases in which the therapy was directed toward sustaining the vasomotor tone. Pituitary was the agent selected. Epinephrine

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<sup>5</sup> Barrach, A. L. Acute Disturbance of Lung Function in Pneumonia, *J. A. M. A.* 89:1865 (Nov. 26) 1927.

was rejected, partly because its action is too transient, and partly because it increases the contraction of the heart muscle<sup>6</sup> Ephedrine was considered, but I did not think that I knew enough about its pharmacologic or its toxicologic actions to justify its use The extent of my observations is not sufficient to warrant definite conclusions, but I believe that they show effects that are suggestive and therefore worth recording

#### DIFFUSIBLE AND OTHER STIMULANTS

In my experience, caffeine is ineffective as a stimulant to the circulation in pneumonia I have never seen any clear evidence that its administration accomplishes any good I have seen patients who had received repeated doses over some time exhibit insomnia and restlessness that amounted almost to delirium, these symptoms subsided when the administration of caffeine was discontinued

The same may be said of stichnine as of caffeine

Camphor administered hypodermically in oil apparently affords a brief period of stimulation, which occasionally tides over a critical period If this effect is not prompt and definite, nothing will be accomplished by repeated dosage

The stimulant effect of ammonia is too weak and too transient to be of material value

Of the benefit derived from whisky, I have a definite empiric conviction Its good effect does not appear in all cases It is valuable for elderly persons, for those habituated to its use, it is more so I am unable to explain entirely its physiologic action Its hypnotic action in a disease in which rest and sleep are so important is undoubtedly valuable, often lessening the need of opium derivatives It induces a sense of comfort and serenity in the patient, which is not a handicap in the fight with the disease Its food value may be a factor, but the quantity administered seems too small for this to explain the whole matter A definite beneficial effect on the pulse is often noted A fuller, softer, more adequate beat replaces the irritable subtonic one In spite of the myriads of pages written on the subject of alcohol, there may still be something to learn about it

The accompanying tables, giving the details of the cases of the series, require further comment Virulence is rated as mild, moderate, severe, severe plus and severe double plus

It was mild in those cases in which there was a definite clinical picture and recorded physical signs establishing the diagnosis of pneumonia but in which the patients were not at any time sufficiently ill to give serious concern as to the outcome of the disease The virulence

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<sup>6</sup> Cushny, A. R. Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1918, p. 368

TABLE 1—Patients Receiving Digitalis on Admission to Hospital

Num ber	Age	Virulence	Maxi- mum Leuko- cyte Count	Days from Onset to Admis- sion	Daily Digitalis Dosage, Gm	Result	Bacteriology of Sputum	Remarks
1	37	Moderate	26,000	2	0.27	R		Empyema, pneumonia followed grip
2	38	Severe	21,000	?	0.3	R	Streptococcus hemolyticus	
3	69	Moderate	19,600	1	0.55 (5 days)	D	Pneumococcus	Hypertension and alcoholism
4	18	Severe	18,600	1½	0.27	R		
5	55	Moderate	26,800	?	0.33	R		
6	19	Severe	32,600	1	0.33	R		
7	35	Severe	7,400	5	0.55	R	Streptococcus hemolyticus and viridans	Diagnosis confirmed by x ray, pleural effusion
8	6	Severe	24,000	?	0.1	R		
9	42	Moderate	13,000	4	0.25	R		
10	37	Severe	24,400	4	0.2	R		
11	66	Moderate	25,000	?	0.33	R		
12	58	Moderate	24,200	7	0.4	R	Streptococcus viridans	
13	28	Severe ++	21,800	1	0.53	R		Complicated by otitis media, phlebotomy seemed life saving
14	84	Severe ++	8,800	1	0.55	D		Died on fourth day
15	52	Severe	17,000	?	0.8	R	Streptococcus hemolyticus and viridans, pneumococcus	Pneumonia followed acute bronchitis of two weeks' duration
16	65	Severe +	27,800	9	0.27	D	Streptococcus viridans and hemolyticus	Admitted in an advanced stage
17	41	Severe +	19,800	2	0.6	D	Pneumococcus and Streptococcus hemolyticus	Pneumococcus on second culture, two days after, Streptococcus hemolyticus
18	27	Severe +	24,000	2	0.4	R	Streptococcus hemolyticus and viridans	
19	30	Severe +	28,600	2	0.6	R		
20	25	Severe +	20,200	1	0.4	R		
21	55	Severe	15,000	4	0.1	R	Streptococcus hemolyticus and viridans	
22	16	Severe +	10,000	4	0.6	R	Streptococcus viridans	Strophanthin, 0.61 mg by hypodermic on admission
23	14	Severe	40,000	5	0.33	R		Empyema
24	21	Severe +	20,200	3	0.8	R	Streptococcus hemolyticus	
25	58	Moderate	16,100	2	1.1	R		
26	14	Severe +	30,000	3	0.4	D	Streptococcus hemolyticus and viridans	Late involvement of opposite lung
27	56	Severe +	40,750	2	0.6	D	Streptococcus hemolyticus and viridans	
28	45	Severe	24,050	?	0.15	R		
29	50	Severe	16,400	6	0.4	D	Streptococcus viridans and hemolyticus	Empyema
30		Severe +	20,200	1	Chart 6	R	Streptococcus viridans, pneumococcus and streptococcus hemolyticus	

Total number of cases, 30, deaths, 7, mortality, 23.33 per cent

TABLE 2—Patients in Whom Digitalis Therapy was Instituted Later than Date of Admission

Num ber	Age	Virulence	Maxi- mum Leuko- cyte Count	Digi- talis Begun, Daily of Dosage, Gm	Result	Bacteriology of Sputum	Remarks	
1	72	Moderate	19,400	3d	0.25	R		
2	55	Severe	33,000	4th	0.2	R		
3	15	Moderate	21,000	4th	2.6	R	Streptococcus hemolyticus	
4	64	Moderate	17,800	4th	0.1	R	Streptococcus viridans	
5	29	Severe	17,200	4th	0.27	R		
6	58	Moderate	27,000	3d	0.27	R		
7	65	Moderate	14,800	4th	0.4	R		
8	59	Severe	26,100	6th	0.63	R		
9	45	Moderate	16,100	5th	0.53	R		
10	31	Severe	23,000	3d	0.4	R	Streptococcus viridans and hemolyticus	
11	78	Moderate	22,600	4th	0.4	R		
12	53	Severe	21,000	2d	0.33	R	Pneumococcus, Streptococcus viridans and hemolyticus	
13	29	Severe	23,200	7th	0.6	R		Relapse on fifth day
14	32	Severe +	18,800	3d	0.1	D	Streptococcus hemolyticus	
15	17	Severe +	38,000	7th	0.6	R		
16	28	Severe	24,400	2d	0.6	R	Pneumococcus and Streptococcus hemolyticus	
17	81	Severe	37,000	2d	0.6	D		Chronic hypertension
18	25	Severe	22,100	3d	0.4	R		
19	16	Severe +	26,600	3d	0.4	R		
20	76	Severe +		2d	0.4	D		
21	58	Severe	24,800	4th	0.4	R		
22	40	Severe		5th	0.4	R		
23	36	Severe +	30,400	6th	0.4	R	Streptococcus viridans and hemolyticus	Phlebotomy and whisky seemed the effective therapy
24	26	Moderate	18,050	2d	0.27	R	Streptococcus viridans and hemolyticus	
25	17	Moderate	36,850	8th	0.8 in 12 hours	R	Streptococcus viridans and hemolyticus	Pituitary (4 doses), with digitalis, im- pending collapse
26	30	Mild	10,400	5th	0.33	R		
27		Moderate	21,000	2d	0.5	R	Streptococcus viridans	
28		Moderate	18,100	8th	0.27	R		
29	67	Severe	22,000	4th	0.2	R		Complicated by
30	34	Severe ++	36,300	2d	Chart 1	D	Streptococcus hemolyticus and viridans	nature of which was not determined Autopsy showed mul- tiple abscesses in both lungs
31	39	Severe	37,850	3d	Chart 2	D	Streptococcus hemolyticus and viridans	Complicated by active secondary syphilis
32	55	Severe +	21,500	2d	Chart 3	D	No sputum	Extremely obese, treated 4 years for hypertension (200+)
33	19	Severe ++	34,950	3d	Chart 4	D	No sputum	Overwhelming intoxi- cation
34	26	Severe ++	19,700	2d	Chart 7	D	Streptococcus viridans and hemolyticus	

Total number of cases, 31, deaths, 8, mortality, 26.53 per cent



TABLE 3—Patients Treated Without Digitalis

Num- ber	Age	Virulence	Maximum Leukocyte Count	Result	Therapy	Bacteriology of Sputum	Remarks
1	27	Mild	15,500	R	Sodium citrate, 8 Gm daily	Pneumococcus	
2	38	Mild	13,000	R	Sodium citrate, 6 Gm daily		
3	18	Mild	18,000	R	Symptomatic	Streptococcus viridans	Pneumonia followed tonsillectomy
4	52	Severe	26,000	R	Diuresis	Streptococcus viridans and Streptococcus hemolyticus	
5	53	Severe	15,800	R	Sodium citrate, 8 Gm daily		
6	58	Mild	22,000	R	Ammonium chloride, whisky, sponge baths		
7	79	Mild	36,000	R	Initial, dovers powder, symp- tomatic		
8		Severe	26,000	R	Initial catharsis, symptomatic		
9	65	Moderate	11,000	R	Sodium citrate	Pneumococcus	
10	18	Severe	37,200	R	Sodium citrate, 8 Gm daily		
11	20	Mild	13,000	R	Creasote, calcium and ammonium salts	Streptococcus viridans	
12	21	Mild	17,800	R	Catharsis, symptomatic		
13	27	Mild	26,000	R	Ammonium chloride, symp- tomatic		
14	32	Mild	18,400	R	Symptomatic	Streptococcus viridans and hemolyticus	
15	75	Mild	16,000	R	Initial, dovers powder, sodium citrate, 8 Gm		
16	16	Mild	22,600	R	Sodium citrate, 6 Gm daily		
17	29	Severe	28,000	R	Symptomatic	Pneumococcus 4, and Streptococcus hemolyticus	
18	21	Severe	21,800	R	Urotropin, creasote		
19	38	Severe	11,400	R	Sodium citrate, 6 Gm daily	Streptococcus hemolyticus and viridans	
20	40	Mild	14,600	R	Urotropin		
21	46	Severe	19,800	D	Catharsis, cough mixture and whisky	Streptococcus viridans and hemolyticus	Followed afebrile bronchitis of ten days' duration
22	14	Severe	24,400	R	Quinine	Streptococcus viridans and pneumococcus	Followed otitis media
23	64	Mild	23,400	R	Initial catharsis, sodium citrate, 4 Gm	Streptococcus hemolyticus and viridans	Diagnosis confirmed by x ray
24	28	Mild		R	Sodium citrate, 12 Gm daily	Streptococcus hemolyticus and viridans	Diagnosis confirmed by x ray
25	38	Moderate	18,800	R	Symptomatic		
26	30	Mild	13,200	R	Symptomatic	Streptococcus hemolyticus and viridans	
27	38	Mild	12,400	R	Symptomatic	Streptococcus hemolyticus and viridans	Followed bronchitis, diagnosis confirm ed by x ray
28		Severe	16,400	R	Sodium citrate	Streptococcus viridans and hemolyticus	Complicated by active syphilis
29	54	Severe +	22,000	D	Sodium citrate, 8 Gm daily, caffeine	Pneumococcus	Obese and unman ageable
30	36	Severe ++		D	Symptomatic		In extremis on admission
31	55	Severe ++	34,600	R	Transfusion	Pneumococcus 2	Blood stream infec- tion
32	65	Severe +	11,350	D	Symptomatic		In extremis on admission
33	37	Mild	12,750	R	Symptomatic	Streptococcus hemolyticus and viridans, Bac mucos capsulat	
34	43	Severe	11,250	R	Sodium citrate, phlebotomy		Diagnosis confirmed by x ray (chart 5)
35	48	Severe	12,700	R	Potassium acetate	Streptococcus hemolyticus and viridans	
36	38	Severe	26,200	R	Urotropin, acetyl- salicylic acid		

Total number of cases, 34, deaths, 8, mortality, 26.53 per cent

was considered moderate in those cases in which the patients were acutely ill at the outset but improved steadily and made an uneventful recovery, and severe in those cases in which serious concern as to the prognosis was felt. Severe plus violence was present in those cases in which the patients were so gravely ill that a fatal issue was expected, and severe double plus in cases in which there was overwhelming intoxication or grave complications.

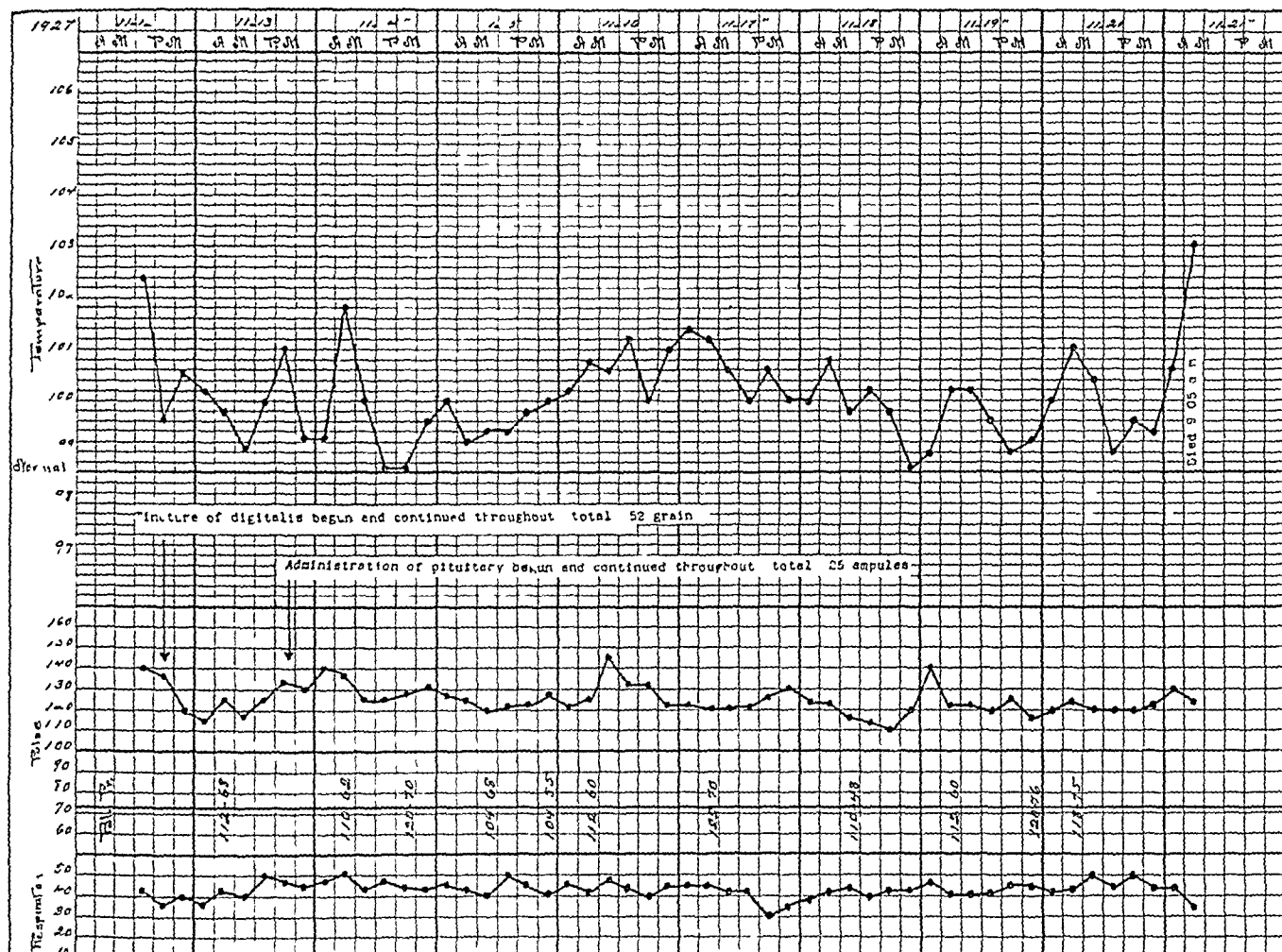


CHART 1 (case 1)—The blood pressure was maintained apparently by the administration of pituitary

A complete presentation of the treatment given these patients could not be made without reporting the individual cases. Alkaline diuretics were used in many cases, the dosage being limited by the appearance of alkaline urine, in a large majority opium derivatives were used at some time for pain, cough or restlessness. Various counterirritants to the chest were frequently used, mustard being the favorite. Occasionally an ice bag was placed on the chest of a patient. A considerable number were given more or less systematic hydrotherapy in the form of sponge baths. Caffeine was used in circulatory failure by nearly all physicians, whether or not digitalis was being given.

In giving the bacteriology of the sputum, I state first the predominating organism and then the others in the order of the number of colonies present

REPORT OF CASES

CASE 1—A man, aged 34, was admitted to the hospital on the second day of the disease, which was severely toxic from the onset. There was pneumonia of the lower lobe of the right lung. Cultivation of the sputum resulted in *Streptococcus hemolyticus* predominating, and *Streptococcus viridans*. The leukocytes

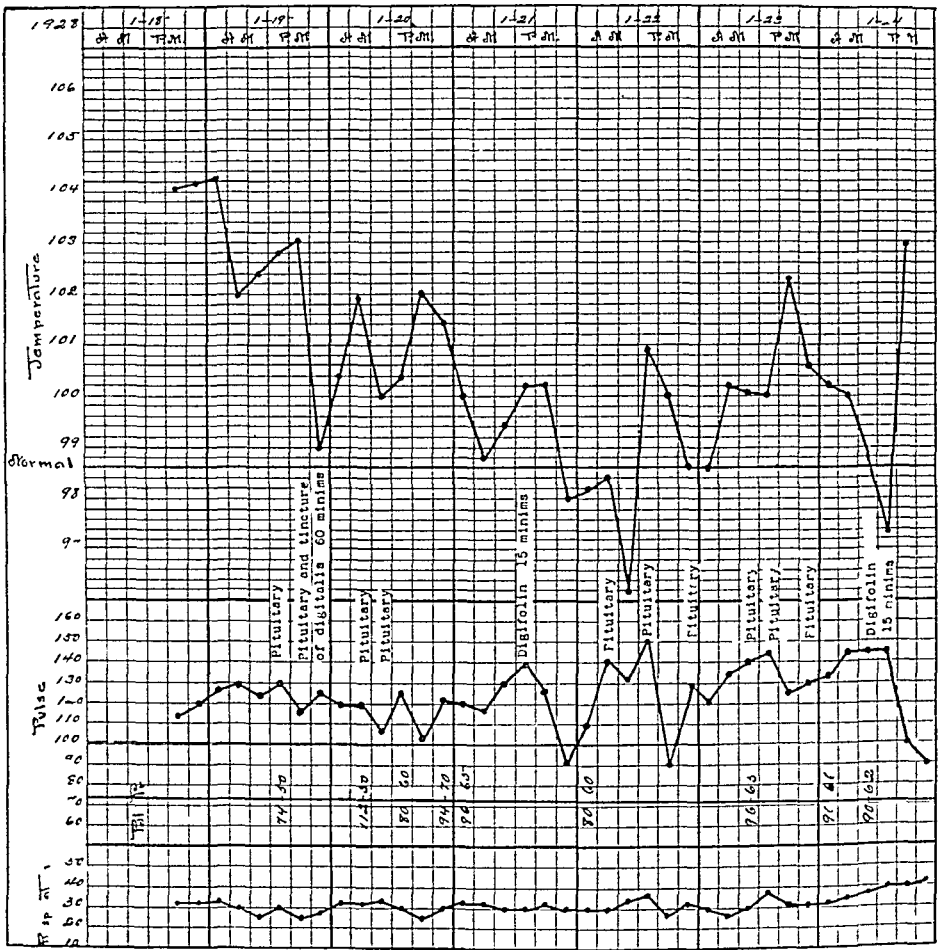


CHART 2 (case 2) —Death occurred from the extension of the disease following effort

numbered 36,300. The patient showed good resistance until the fifth day, at which time invasion of the left lung was noted. He was treated with digitals and pituitary, receiving 33 grains (2.16 Gm) of the former and 16 ampules of the latter. It was noted that his blood pressure was well sustained until the day of death, which occurred on the twelfth day. Autopsy showed bronchopneumonia of both lungs, with multiple small abscesses, also active tuberculosis of both upper lobes, a recent recrudescence (chart 1).

CASE 2—A man, aged 39, was admitted to the hospital on January 18. The evening before he was admitted, he was seized with pain in the right side of the chest, cough and weakness. He was found to have pneumonia involving the middle

lobe of the right lung and the lower lobe of the left lung, and also an abundant eruption of secondary syphilids. The blood showed leukocytes, 35,850, with 90 per cent polymorphonuclears. The Wassermann reaction was 4 plus. The blood culture was negative. A sputum culture showed *Streptococcus viridans* predominating and *Streptococcus hemolyticus*. The extremely low blood pressure which existed on admission seemed to respond favorably to the administration of

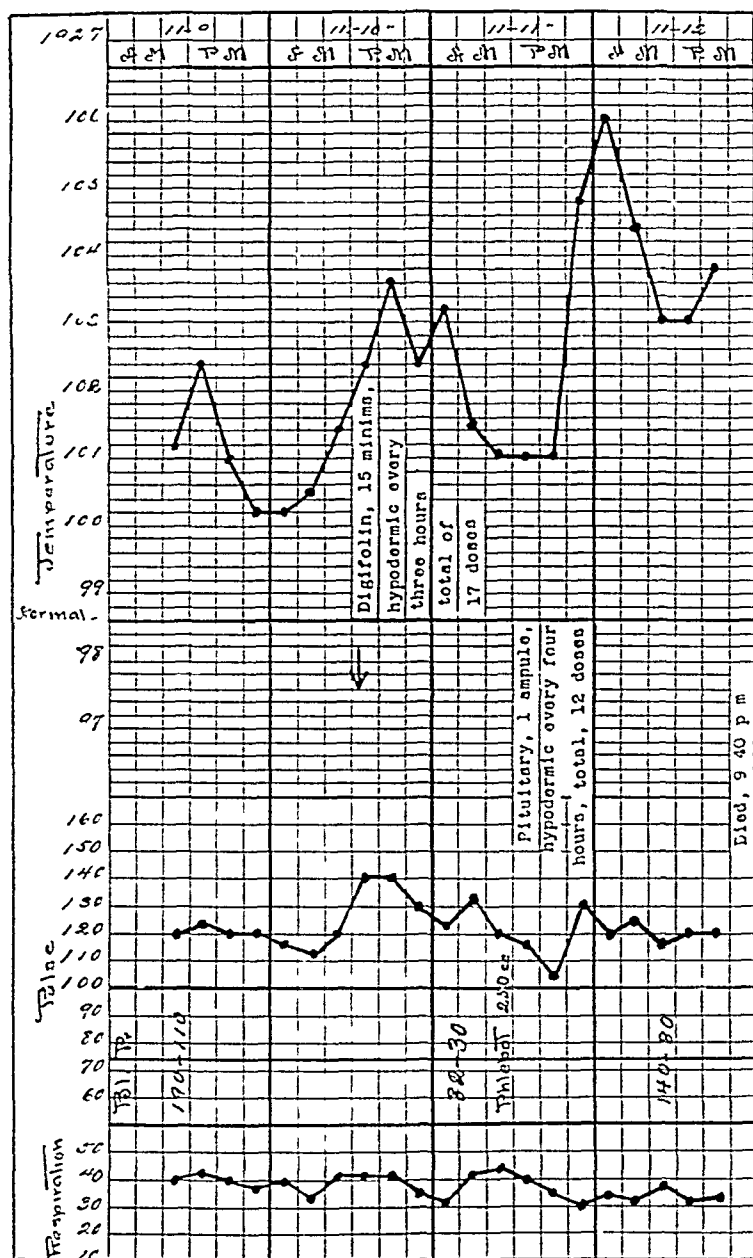


CHART 3 (case 3)—Death occurred from toxic respiratory paralysis, the heart function was maintained

pituitary. On the fourth day, he appeared to be doing well, and I ordered an x-ray picture made of the lungs. During this procedure, he was subjected to more effort than is usual in such cases, and this was promptly followed by an invasion of the lower lobe of the right lung, which proved fatal. Autopsy showed pneumonia of the middle lobe of the right lung and the lower lobes of both lungs, while the x-ray picture did not show any involvement of the lower lobe of the right lung.



nuclears Treatment with a digitalis preparation was begun on the second day. There was little change in her condition until the third day, when she went into collapse, with a rapid fall of blood pressure A phlebotomy was done, and pituitary treatment was instituted She appeared to be dying at the time, but rallied, and survived until the following day, when she died of respiratory failure In this case the inhalation of oxygen was effective in improving the dyspnea and cyanosis for a time (chart 3)

CASE 4—A robust young mechanic, aged 19, was admitted to the hospital on February 17 He was too ill to give a history, and none was obtainable He had

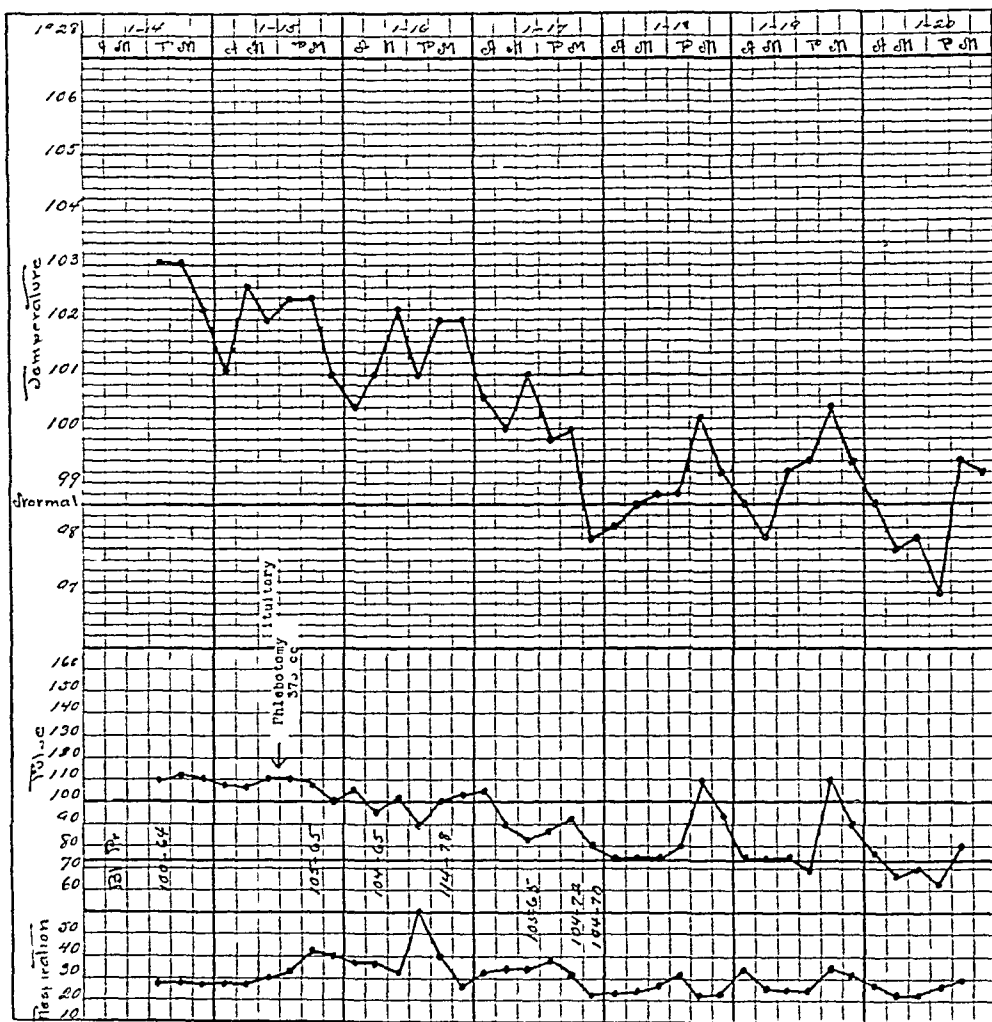


CHART 5 (case 5) —The patient was evidently benefited by early phlebotomy

worked until thirty-six hours before admission He had pneumonia of the lower and middle lobes of the right lung The leukocytes numbered 34,950, with 89 per cent polymorphonuclears The urinary chlorides were absent He had a harassing cough, but did not raise any sputum Marked dyspnea and cyanosis were present It was manifest from the outset that an overwhelming intoxication was present He died on the fourth day after admission Autopsy was refused

Phlebotomy gave temporary relief from the dyspnea The day before death there were signs of invasion of the left lung At the same time evidence of beginning myocardial failure was noted, namely, a diffuse wavelike impulse and a diminution of the muscular tone of the heart sounds In spite of the malignant

character of the infection, pituitary seemed to maintain the blood pressure at a higher level than that shown when he was admitted (chart 4)

CASE 5—A white man, aged 42, was admitted to the hospital on the third day of the disease, he was severely toxic, with great distress in breathing. There was pneumonia of the upper and middle lobes of the right lung. The leukocytes numbered 11,250. The sputum showed streptococci, but no pneumococci. Conspicuous subjective relief followed phlebotomy. The patient's circulation did not require supportive treatment after the second day in the hospital. Chart 5 shows

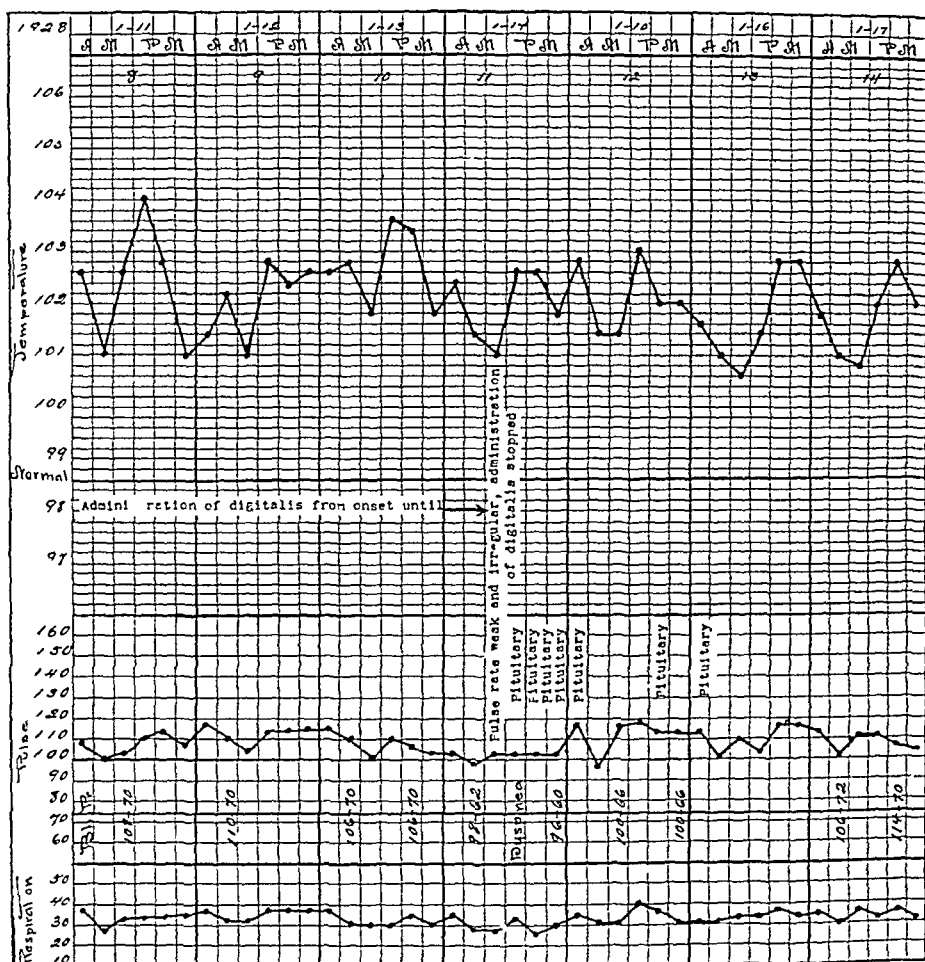


CHART 6 (case 6)—The patient had received digitalis therapy, the critical phase improved after this therapy was discontinued

only the acute phase of his illness, the convalescent phase being omitted. He made a complete recovery, though resolution was somewhat delayed.

CASE 6—A woman, aged 23, seen in consultation with Dr. Hornaday, was admitted to the hospital on January 4, with pneumonia of the middle and lower lobes of the right lung. The condition was severe from the onset. The leukocytes numbered 16,300. A sputum culture showed *Streptococcus viridans* predominating, also *Streptococcus hemolyticus* and pneumococcus. The total febrile period in this case was fifty-eight days. There was delayed resolution, and in the later weeks there was a complication of pleural effusion which required repeated withdrawal. Examination of the fluid exhibited the presence of tuberculosis. Only a segment of the chart is submitted, namely, the portion covering the eighth to the sixteenth

day (chart 6) The patient received digitalis from the outset,  $4\frac{1}{2}$  grains (0.29 Gm) daily for two days, and then 6 grains (0.4 Gm) daily until the eleventh day She began to show evidence of weakening circulation on the eighth day, at which time a single dose of pituitary was given On the tenth day she was worse, and the prognosis was grave On the eleventh day, the use of digitalis was discontinued, and vigorous administration of pituitary was instituted Chart 6 shows the results

The patient made an ultimate recovery This case shows that a circulation which is failing under digitalis therapy may become reestablished when that therapy is discontinued

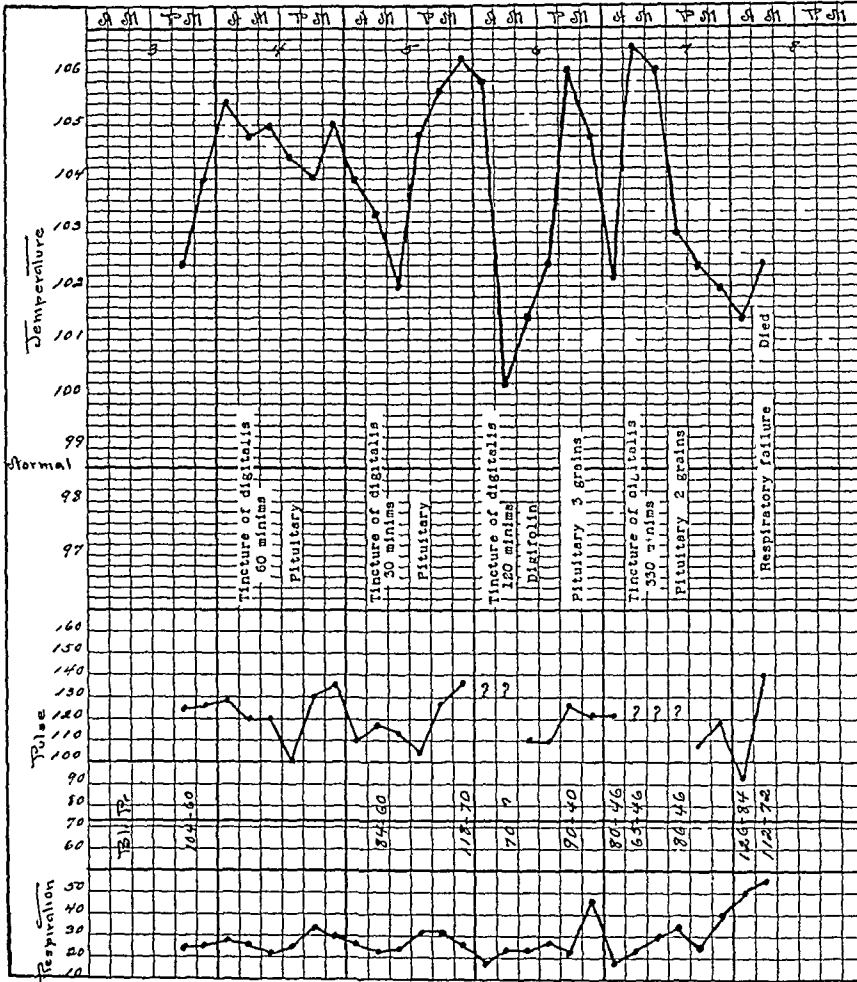


CHART 7 (case 7) —Death occurred as a result of toxic respiratory paralysis, the heart function was maintained throughout

CASE 7—A robust woman, aged 26, mother of seven children, at the time the present illness began was nursing an infant, aged 5 months Three days before admission she began to have pains in the chest and back The next day she had a severe chill, which was followed by fever On that day and the next she had nausea and vomited She was admitted to the hospital on the second day after the chill, extremely ill, cyanosed and with a bright red, sharply defined flush on both cheeks There was severe cough, and she had pain in the right side of the chest Physical examination indicated consolidation of the lower lobe of the right lung and slight enlargement of the liver and spleen The leukocytes numbered



19,800, with 88 per cent polymorphonuclears. There was a bloody expectoration, which on culture showed *Streptococcus viridans* and *Streptococcus hemolyticus*.

Early in the morning of the sixth day she had a collapse, accompanied by profuse sweating, and a pulse rate so rapid, weak and irregular that it could not be counted accurately. There was also Cheyne-Stokes breathing. I thought at the time that I was dealing with the crisis of a pneumococcus infection, as I had not yet received the report from the sputum culture. Under stimulation there was a temporary improvement in the circulatory efficiency, but the patient died on the eighth day after the onset of respiratory failure. Dr. Moore, house physician, was present at the death, and noted that the heart continued to beat for some time after the respiration had finally ceased. He did not time this period, but estimated that it must have been nearly half a minute (chart 7).

The entire clinical picture presented by this patient, except the temperature curve, was identical with that observed in pneumococcus pneumonia.

At autopsy, pneumonia of the lower and upper lobes of the right lung was found. There were also toxic hepatitis, a mild acute splenic tumor, toxic nephrosis, toxic myocarditis and terminal dilatation of the heart on both sides. There was a terminal hypostatic congestion of the left lung. A blood culture from the central portion of the pneumonic area showed a pure culture of *Streptococcus viridans*.

#### CONCLUSION

It is realized that much of the matter presented in this article is an expression of opinion, and as such is open to question. My chief purpose in this paper is to question the opinions which are commonly accepted.

It is possible that the difference in the bacteriology of my cases from that of most cases of pneumonia reported may be a factor in the difference in the reaction to therapeutic measures. The behavior of the circulation in pneumococcus pneumonia, however, has not led me to consider the involvement of that system as materially different from that which seems to occur in streptococcus pneumonia.

An important difference is that in inflammation of the lungs caused by streptococci one is not dealing with an eight day infection which can be expected to terminate by crisis at a given time. The duration is inconstant and the defervescence is gradual (as a rule), extension of the disease and relapse may occur at almost any stage. The therapeutic problem, therefore, is not merely the sustaining of the vitality of the patient till a definite crisis is passed. This fact seems to make conservatism in the use of myocardial stimulants more important.

To attempt to combat the collapse of the peripheral circulation seems to be a sound principle in the therapy for pneumonia. My observation has not been sufficiently extensive to speak positively of the value of pituitary for this purpose. I believe that something beneficial has been accomplished in some patients, and this opinion is shared by others who have been associated with me. It manifestly does not have a beneficial effect on the toxemia. So far I have not seen any ill effects that I could attribute to the drug.

# IMPAIRED AURICULOVENTRICULAR CONDUCTION IN RHEUMATIC FEVER

A COMPARATIVE STUDY WITH DIAGNOSTIC APPLICATIONS<sup>1</sup>

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It is now well known that auriculoventricular conduction is frequently impaired in the course of rheumatic fever and that this disturbance affords valuable evidence of myocardial involvement<sup>1</sup>. In a number of instances of partial or complete heart block<sup>2</sup> and in one case showing only prolonged auriculoventricular conduction,<sup>3</sup> post-mortem examination of the heart has disclosed characteristic rheumatic lesions involving the auriculoventricular node or bundle. Such lesions have consisted of cellular infiltration and edema during the acute stages of the disease, or of scar tissue after healing has taken place. The transitory nature of conduction disturbances in many cases indicates that the inflammatory process may subside without graphic evidence of permanent damage to the heart muscle.

In following a series of cases of rheumatic fever in which frequent electrocardiograms were made, the diagnostic importance of disturbances in auriculoventricular conduction became apparent. The present study covers a period of nine years. Most of the patients had arthritis; some were predominantly of the cardiac type. The records of all rheumatic patients showing prolonged auriculoventricular conduction or heart block (partial or complete), as shown in the files of the cardiographic laboratory, were critically analyzed. The P-R interval

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<sup>1</sup> Submitted for publication, Oct. 12, 1928.

<sup>2</sup> From the Department of Medicine, College of Physicians and Surgeons of Columbia University, and the Presbyterian Hospital.

\* Read at the meeting of the American Society for Clinical Investigation, Washington, D. C., April 30, 1928.

1 Parkinson, J., Gosse, A. H., and Gunson, E. B. The Heart and Its Rhythms in Acute Rheumatism, *Quart J Med* **13**:363, 1919-1920. Cohn, A. E., and Swift, H. F. Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, *J Exper Med* **39** 1, 1924.

2 Gerhardt, D. Ueber Ruckbildung des Adams-Stokes'schen Symptomkomplexes, *Deutsches Arch f klin Med* **93** 485, 1908. Bramwell, B. A Case of Heart Block with Fibrous Degeneration and Partial Obliteration of the Bundle of His, *Brit M J* **1** 995, 1909. Butterfield, H. G. Acute Carditis and Heart Block, *Heart* **3**:203, 1911-1912. Naish, A. E., and Kennedy, A. M. Heart Block in Acute Rheumatic Carditis, *Lancet* **2** 1242, 1914.

3 Cowan, J., Kennedy, A. M., Patterson, A. R., and Teacher, J. H. Two Cases of Acute Endocarditis, *Quart J Med* **4**:35, 1910.

was considered prolonged if it exceeded 0.2 second. Cases in which digitalis or quinidine was given during the time of observation were excluded. Salicylates and drugs of the cinchophen group were given to most of the patients. Although it has been shown that salicylate in certain cases of prolonged conduction appears to exert an effect in shortening the P-R interval,<sup>4</sup> it is believed that this action did not materially modify the results of the analysis. Electrocardiograms were taken in most cases at least once a week during the stay in the hospital and often daily during the acute phases of the disease. Follow-up examinations at varying intervals were also made.

For purposes of comparison, all other cases showing disturbances in auriculoventricular conduction were similarly reviewed. It is fair to state that in the nonrheumatic patients, graphic records usually were

TABLE 1—Data in One Hundred and Forty-Five Cases Showing Disturbances in Auriculoventricular Conduction

	Total Cases	Total Cases, per Cent	Long P R	Incomplete Block	Complete Block	Long P R and Block at Different Times
Rheumatic fever	78	53.8	76	6	0	4
Arteriosclerotic and hypertensive heart disease	42	28.9	29	5	8	0
Syphilitic heart disease	10	6.9	8	1	1	0
Nonhemolytic streptococcus endocarditis	3	2.1	3	0	0	0
Miscellaneous	12	8.3	11	1	1	1
Total	145	100.0	127	13	10	5

taken at less frequent intervals. When the criteria mentioned were employed, a total of 145 cases was found in all groups. Of these, 127 showed a prolonged P-R interval. The importance of the latter observation as will be pointed out, should particularly be stressed.

#### ANALYSIS OF MATERIAL

In a comparison of the incidence of impaired auriculoventricular conduction in the various clinical conditions in which it was encountered, certain striking contrasts are at once apparent (table 1). More than half (53.8 per cent) of the cases were instances of rheumatic fever. Next in numerical importance was the group including patients with arteriosclerotic and hypertensive heart disease (28.9 per cent). These were considered together for convenience in discussion and because the borderline between them is often ill-defined. The syphilitic cases comprised 6.9 per cent of the total and the cases of nonhemolytic strepto-

<sup>4</sup> Levy, R. L., and Turner, K. B. Variations in Auriculoventricular Conduction Time in Rheumatic Carditis with Salicylate Therapy, *Proc. Soc. Exper. Biol. & Med.* 25: 64, 1927.

coccus endocarditis only 2.1 per cent. In the miscellaneous group, which formed 8.3 per cent of the cases, were the following: hyperthyroidism, one case, hypothyroidism, one; diphtheria, one; *Staphylococcus aureus* bacteremia, one; chronic nephritis, one; congenital heart disease, one; acute tonsillitis, three; unknown two. The three cases of acute tonsillitis are worthy of special mention. In them, prolonged conduction was found during or shortly after the attack, without other signs of disease. It is possible that in these patients, early myocardial involvement, perhaps due to rheumatism, was detected in the graphic records. Further studies along these lines are in progress.

In rheumatic fever, prolonged auriculoventricular conduction is by far the most frequent disturbance, whereas in the arteriosclerotic-

TABLE 2—*Relative Frequency of Prolonged Auriculoventricular Conduction (Without Block) in One Hundred and Twenty-Seven Cases*

	Total Cases	Per Cent
Rheumatic fever	76	59.9
Arteriosclerotic and hypertensive heart disease	29	22.8
Syphilitic heart disease	8	6.3
Nonhemolytic streptococcus endocarditis	3	2.3
Miscellaneous	11	8.7
Total	127	100.0

TABLE 3—*Incidence of Prolonged Auriculoventricular Conduction in Rheumatic Fever in Four Hundred and Three Cases*

P-R prolonged		112 (27.8%)
No digitalis	60 (14.9%)	
Received digitalis	52 (12.9%)	

hypertensive group, partial or complete heart block is relatively more common. In the remaining groups, as in rheumatism, a prolonged P-R interval is the more frequent observation.

From a study of table 1, then, it is established that conduction disturbances in the heart are observed much more often in rheumatic fever than in any other condition, and that lengthening of the P-R interval is the most important of these disturbances. The latter point is further emphasized in table 2.

If prolongation of auriculoventricular conduction is found more frequently in rheumatism than in other diseases, in what proportion of rheumatic patients is this evidence of myocardial involvement present? Of 403 cases of rheumatic fever observed electrocardiographically 112 (27.8 per cent) showed a long P-R interval (table 3). Fifty-two (12.9 per cent) of these patients received digitalis in amounts which, it appears likely, were insufficient to affect auriculoventricular conduction. Other figures on the incidence of impaired conduction in rheumatism are

available. Thus, 87 per cent of Swift's cases<sup>5</sup> showed an increase in P-R time or incomplete block. The higher incidence in this series is due in part to the use of a less rigid criterion for prolongation and in part to the fact that only patients with the more severe forms of rheumatism were admitted to the Rockefeller Hospital. The figure reported from Mt. Sinai Hospital, New York,<sup>6</sup> 27.6 per cent, is more nearly like our own. It is based on a similar criterion for prolongation (0.2 second or over) and probably represents the average incidence in a general medical service.

The figure for the incidence of prolonged auriculoventricular conduction in subacute bacterial endocarditis is based on a small number of cases. In twenty-three patients, a long P-R time was found in three (13 per cent). In Libman's series of sixty-one cases,<sup>6</sup> prolonged conduction was observed in 16 per cent. It is, of course, possible that in

TABLE 4—*Sex and Age of One Hundred and Thirty Patients Showing Disturbances in Auriculoventricular Conduction*

	Total Cases	Male	Female	Age	
				Range	Average
Rheumatic fever	78	51	27	7-56	27.4
Arteriosclerotic and hypertensive heart disease	42	27	15	35-82	60.2
Syphilitic heart disease	10	8	2	32-55	49.0
Total	130	86	44		

some of these a mixed infection was present, i. e., bacterial and rheumatic.

The sex and age of patients with impaired auriculoventricular conduction are shown in table 4. In rheumatic, arteriosclerotic-hypertensive and syphilitic groups, males predominate. In the first two groups, the ratio is about 2:1. The average age in each group approximates that at which the various diseases are most frequently encountered—rheumatism in the young, syphilitic heart disease in middle age and vascular degeneration in advancing years.

A correlation of conduction disturbances with other changes in the form of the electrocardiogram has not been attempted. In the rheumatic cases, lengthening of auriculoventricular conduction has, in general, been accompanied by leukocytosis (i. e., a white cell count of more than 10,000). The average counts ranged around 14,000 to 15,000 white cells per cubic millimeter. This parallelism was to be

5 Swift, H. F. Rheumatic Fever, *Am. J. M. Sc.* **170**: 631, 1925.

6 Rothschild, M. A., Sacks, B., and Libman, E. The Disturbances of the Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever, *Am. Heart J.* **2**: 356, 1927.

anticipated, since both a long P-R interval and leukocytosis are signs of active infection in the heart muscle. In five cases showing prolonged conduction the white cell count was normal.

#### DIAGNOSTIC APPLICATIONS

*Impaired Auriculoventricular Conduction as an Aid in Differential Diagnosis*—If, then, prolonged conduction is more frequent in rheumatic fever than in any other disease, and this group of patients is distinguished by age limitations, the following diagnostic aphorism may be formulated: a prolonged P-R interval or heart block occurring in a person under the age of 35, who is not syphilitic and who has not taken digitalis, affords presumptive evidence of the presence of rheumatic carditis. On rare occasions, the differentiation between rheumatism and subacute bacterial endocarditis may be difficult. Often, the diagnosis of the rheumatic nature of a cardiac disturbance can be made in the absence of the usual criteria. The following case illustrates this point.

A young married woman, aged 26, while climbing in Switzerland six weeks prior to her visit to one of us, noted palpitation and dyspnea. During the next few days, these symptoms recurred several times. Two weeks later, in London, she had acute tonsillitis. Four days before our examination, she arrived in New York, exhausted and with a temperature of 101 F. The leukocyte count was 15,000. Her physician suspected infection of a sinus, but because of the presence of tachycardia and an apical systolic murmur, requested a cardiac examination. Pain in the joints, chills or sweats had not occurred.

The heart was normal in size, the rate was 116 per minute at rest. A blowing, mitral systolic murmur was present. An electrocardiogram showed a P-R interval of 0.25 second, without other changes. A diagnosis was made of rheumatic carditis. Ten days later, severe, generalized arthritis developed, yielding promptly to medication with salicylate. Six weeks after the patient was first seen, the conduction time was 0.2 second. Tonsillectomy was done. The patient has been well for four years, and there is now no evidence of cardiac damage.

In rare instances, heart block may be the first sign of rheumatic fever, as in the patient reported by White.<sup>7</sup> Such a patient recently came under our observation.

A housewife, aged 42, was admitted to the hospital complaining of shortness of breath, which had been noted on exertion for six months and which was becoming progressively worse. For nine days she had been in bed, but without medication.

She had scarlet fever at the age of 27. During adult life she suffered from severe tonsillitis on four occasions, the last attack having occurred six months before admission to the hospital. There was no history of pain in the joints or chorea.

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<sup>7</sup> White, P. D. Acute Heart Block Occurring as the First Sign of Rheumatic Fever, *Am J M Sc* **152** 589, 1916.

Examination on admission showed an obese woman. The temperature was 100.4. The tonsils were moderately large and red. The heart was not enlarged. The rhythm was irregular. There was a systolic murmur over the entire precordium. The peripheral vessels were soft. The blood pressure was 122 systolic, 95, diastolic. The leukocyte count was 13,300. The Wassermann reaction on the blood was negative.

An electrocardiogram taken the following morning showed incomplete heart block, and based on this observation a diagnosis of rheumatic carditis was made. The temperature on this day rose to 101.2.

On the morning of the third day in the hospital, the ankles and wrists became painful, red and swollen. The temperature was 102. Medication with salicylate was begun in doses of 8 Gm daily. There was prompt relief from the arthritis and a fall in temperature.

The administration of salicylate was continued. Seventeen days after admission, dropped beats were no longer present, although P-R (conduction) time was still 0.28 second. Four weeks after admission, normal conduction time (0.16 second) was recorded for the first time. Five days later, because the patient felt

TABLE 5—*Persistence of Prolonged Auriculoventricular Conduction in One Hundred and Twenty-Seven Cases*

	Total Cases	Only One Record	Temporary	Permanent*
Rheumatic fever	76	18	45	13
Arteriosclerotic and hypertensive heart disease	29	19	3	7
Syphilitic heart disease	8	6	1	1
Nonhemolytic streptococcus endocarditis	3	1	0	2
Miscellaneous	11	4	4	3
Total	127	48	53	26

\* Permanent in the sense of denoting the period of observation. The duration of this period was, of course, variable.

well, she left the hospital against advice, still taking acetylsalicylic acid. One month later, she reported for follow-up examination. Conduction time was normal (0.17 second), and she did not have any complaints.

In this case, incomplete heart block gave the clue to the rheumatic etiology of the condition twenty-four hours before arthritis appeared. The block persisted for seventeen days and prolonged auriculoventricular conduction for another eleven days. The systolic murmur over the precordium was the only sign of possible valvular involvement.

*Prolonged Conduction as Evidence of Persistent Cardiac Involvement*—Although often transitory during the acute stages of the disease, prolonged conduction may continue for months, long after the other manifestations of rheumatic fever have subsided. In the great majority of cases it tends eventually to return to within normal limits, in a few, prolongation is permanent, probably due to fibrotic changes in the region of the auriculoventricular node or bundle. In table 5, the persistence of prolonged auriculoventricular conduction is shown in the various disease groups. In the arteriosclerotic-hypertensive group, permanent changes in conduction are relatively frequent, and result in partial or complete heart block.

The following case illustrates the value of graphic records in the detection of persistent myocardial lesions in rheumatic fever

A trained nurse, aged 50, had her first attack of rheumatic fever following tonsillitis, two months before admission to the hospital. The heart was slightly enlarged, and a mitral systolic murmur was audible. The P-R interval was 0.32 second. After the patient had been in bed for a week the temperature, pulse and joints were normal and remained so, except for a slight flare-up after tonsillectomy. This was performed seven weeks after admission. The conduction time remained long (from 0.35 to 0.21 second) during the four months the patient was in the hospital and for five months thereafter (nine months in all), during which period a regimen of rest was conscientiously carried out. At the end of this time the P-R interval was found to be 0.17 second, and the patient returned to work. She has been well and working steadily for the past three years. The heart is still a little enlarged. There is no evidence of valvular disease or myocardial insufficiency.

#### SUMMARY

1 Disturbances in auriculoventricular conduction are found more frequently in rheumatic fever than in any other disease. Delayed conduction, as evidenced by prolonged P-R time, is much more common than heart block. These disturbances are usually transitory.

2 In arteriosclerotic and hypertensive heart disease, impaired conduction is encountered next in order of frequency. In this group of cases, heart block is relatively more common. The disturbances in conduction tend to become permanent.

3 In rheumatic fever, as seen in a general medical service, about 27 per cent of the cases show prolonged auriculoventricular conduction. This condition is usually, though not invariably, accompanied by leukocytosis during the active stages of the disease.

4 A prolonged P-R interval or heart block occurring in a person under the age of 35, who is not syphilitic and who has not taken digitalis, affords presumptive evidence of the presence of rheumatic carditis. This sign is often useful in establishing the rheumatic nature of a cardiac disturbance, in the absence of other criteria.

5 Prolongation of auriculoventricular conduction may persist and give evidence of myocardial lesions in rheumatic fever long after the other clinical manifestations of the disease have subsided.



# CULTURAL AND SEROLOGIC REACTIONS WITH GREEN-PRODUCING MICROCOCCI FROM MEASLES\*

N S FERRY, M D  
AND  
ARLYLE NOBLE, A B  
DETROIT

During the past few years several papers have appeared with definite detailed descriptions of green-producing micrococci, obtained from measles, which were considered more or less closely associated with the etiology of the disease. From these original descriptions, it is apparent that the organisms differ from one another in many respects, although the impression has been given and the statement made by several writers that they are similar.

The present study was undertaken in an attempt to arrive at some definite conclusion, if possible, in regard to the relationship of these organisms to one another, and to determine, if they differ, wherein their fundamental differences lie, for the ultimate purpose of determining their relationship to measles.

The first mention of a green-producing micrococcus found frequently associated with measles was in 1917, by Tunnichliff.<sup>1</sup> This organism was described by the author as a green-producing diplococcus that was isolated from the blood, throat and eyes in early cases of measles. "In smears from the original culture, the organism appears as a very small, round, sometimes flattened diplococcus or in short chains, sometimes as clumps of cocci of varying size." Tests for the production of toxin were not mentioned in this original article by Tunnichliff, but later,<sup>2</sup> it seems apparent, she was convinced that it was not a true toxin producer as evidenced by the following statement: "The skin reaction to the diplococcus found by me in measles has been studied with a view to obtaining light on its relation to measles. Berkefeld W filtrates of aerobic and anaerobic cultures, grown from twenty-four hours to six days in broth with and without ascites fluid, failed to produce any reaction." When she prepared killed broth culture antigens, containing the whole culture, she was able, at the same time, to produce skin reactions in a dilution of

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\* From the Medical Research Laboratories, Parke, Davis and Company

\* Read before the American Association of Immunologists, Washington, D C, May 1, 1928

1 Tunnichliff, R. The Cultivation of a Micrococcus from Blood in Pre-eruptive and Eruptive Stages of Measles, *J A M A* 68 1028 (April 7) 1917

2 Tunnichliff, R. Further Studies on a Diplococcus in Measles. A Measles Skin Reaction, *J Infect Dis* 37 193 (Sept) 1925

1 40 This reaction, however, could not be attributed solely to the filtrate. The organisms themselves must have played a large part in the phenomenon, in fact, Tunnichiff himself spoke of this antigen in a later article<sup>3</sup> as an "intracellular toxin."

In March, 1926, Ferry and Fisher<sup>4</sup> described "a small Gram-positive aerobic green-producing streptococcus appearing both in pairs and in chains, which produces an extracellular or soluble toxin specific to measles." In June and December, 1927, this work was given more in detail by Ferry<sup>5</sup> and later experiments with the organism and its toxin and antitoxin were described. Measles toxin has been readily produced with this organism in broth with or without ascites fluid or blood, and typical specific skin reactions have been demonstrated in man following intradermal injections of 0.1 cc doses of from 1:400 to 1:600 dilutions of this toxin. Horses have been immunized with this toxin, giving a specific antitoxin which possesses a definitely measurable potency. In a paper by Ferry and co-workers,<sup>6</sup> results were reported which showed the clinical response to this antitoxin among patients susceptible to measles in comparison to the response of similar patients to measles convalescent serum under the same conditions and on the same wards.

In May, 1926, Hibbard and Duval<sup>7</sup> found a "small Gram positive coccus which was noted in culture tubes that contained semisolid plasma or hydrocele fluid. The micro-organism occurred singly or in pairs and short chains. Subsequently a good growth of the coccus was obtained upon ordinary blood agar plants, and under aerobic conditions at 37 C incubation. A comparative cultural study of the various isolations revealed their complete correspondence with one another and the coccus described by Tunnichiff." With 0.2 cc of a 1:10 dilution of a broth filtrate of this organism, Musser<sup>8</sup> produced a characteristic skin reaction claimed to be indicative of a toxin. Just prior to this, Tunnichiff<sup>3</sup> also

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3 Tunnichiff, R., and Taylor, R. E. Skin Tests in Measles, *J. A. M. A.* **87** 846 (Sept 11) 1926

4 Ferry, N. S., and Fisher, L. W. Measles Toxin. Its Preparation and Application as a Skin Test, as an Immunizing Agent, and for the Production of an Antitoxin, *J. A. M. A.* **86** 932 (March 27) 1926

5 Ferry, N. S. Etiology of Measles, *Am. J. Pub. Health* **17** 565 (June) 1927, Studies on the Etiology of Measles, *Cincinnati J. M.* **8** 191 (June) 1927, Recent Experimental Work on the Etiology of Measles, *Nation's Health* **9** 51 (Dec.) 1927

6 Ferry, N. S., Gordon, E. J., Munro, F. W., Steele, A. H., and Fisher, L. W. Clinical Results with Measles Toxin and Antitoxin, *J. A. M. A.* **91** 1277 (Oct 27) 1928

7 Hibbard, R. J., and Duval, O. W. Studies Upon the Virus of Measles, *Proc. Soc. Exper. Biol. & Med.* **23** 853 (June) 1926

8 Musser, J. H. Studies on Immunity to Measles, *Proc. Soc. Exper. Biol. & Med.* **24** 518 (March) 1927

produced a skin reaction with a 1:10 dilution of a broth filtrate prepared from diplococcus. In this respect, the organisms of Hibbard and Duval and of Tunnichliff are similar in that they produce a filtrate which stimulated a skin reaction in a dilution of 1:10.

In May, 1927, Park, Williams and Wilson,<sup>9</sup> in a paper in which they attempted to determine the relation of the Tunnichliff and Ferry organisms to measles, described several different green-producing micrococci which they had obtained from measles, among which were some similar to the Tunnichliff diplococcus and some similar to the Ferry streptococcus. In regard to the production of toxin these authors stated, relative to the Ferry and Tunnichliff organisms, "in our hands both cultures make a toxin, but that from Ferry's culture is much stronger."

In October, 1927, Cary and Day<sup>10</sup> described a green-producing aerobic gram-positive diplococcus which seemed to be differentiated from other ordinary green producers by its reaction on salicin.

The work here presented is based on a study of the cultural and serologic relationship between the various strains of green-producing micrococci isolated from cases of measles and between these and similar micrococci from other sources. The organisms examined were: Four cultures furnished by Dr. Tunnichliff, blood 1, throat 2, nose 3 and sputum 7, three cultures from Dr. Duval, numbers 1, 2 and 3, one from Dr. Cary, number 47, two from Dr. Park, R 83 and "Tunnichliff", four Ferry, 01860, 01933, 01934 and 01935, and six nonmeasles cultures, 01873 (endocarditis), 01885 (blood culture, infected glands), 01890 (Vincent's disease of the gums), 01966 (acute tonsillitis), 01983 (pyorrhea) and 01987 (acute endocarditis).

With these organisms the following reactions were studied: (1) morphologic and cultural reactions on various mediums, (2) cross-agglutination, agglutinin absorption and complement-fixation reactions with rabbit immune serums, and (3) agglutination, agglutinin absorption and complement-fixation reactions with measles convalescent serums.

#### MORPHOLOGIC AND CULTURAL REACTIONS

The morphologic and cultural characteristics of fourteen so-called measles cultures, isolated by various workers, are summarized in table 1.

For morphologic study, the organisms were grown for eighteen hours on whole blood agar (defibrinated rabbit blood, 0.2 per cent dextrose,  $p_H$  7.6) and in broth (fresh veal infusion broth, 1 per cent Witte's peptone, 0.5 per cent sodium chloride, 0.1 per cent dextrose,  $p_H$  8). Smears

<sup>9</sup> Park, W. H., Williams, A. W., and Wilson, M. The Relation of the Tunnichliff and Ferry Diplococci to Measles, *Am. J. Pub. Health* **17**:460 (May) 1927.

<sup>10</sup> Cary, W. E., and Day, T. A. The Etiology of Measles, *J. A. M. A.* **89**:1206 (Oct. 8) 1927.

TABLE 1—*Morphology and Cultural Reactions of Green-Producing Micrococci from Menstrues*

	Morphology			Growth on Blood Agar	Broth	Litmus Milk	Carbohydrates—Holman's Mediums					
	Blood Agar	Broth	Lactose				Mannit	Salein	Saccharose	Inulin	Control	
Ferry 01860, 01933, 01931, 01935	Gram positive coccus, small, in pairs and short chains, in water of con- densation, longer chains	Majority of organisms in chains (1-10)	Small, smooth colony with wide green zone	Uniform cloud	Marked acid Coagulation ¾ reduced Color returns 10-11 da	Marked acid 16 hrs 18 hrs ¾ reduced 3 da Color returns 10-11 da	Marked acid 16 hrs	Nega- tive	Nega- tive	Marked acid 16 hrs	Nega- tive	Nega- tive
Oary 17	Same as Ferry	Majority of organisms in chains (1-10)	Small, smooth colony with wide green zone	Uniform cloud	Marked acid Coagulation ¾ reduced Color returns 10 11 da Acid and coag- ulation Partial reduc- tion 3 da	Marked acid 16 hrs 18 hrs ¾ reduced 3 da Color returns 10 11 da	Marked acid 16 hrs	Nega- tive	Nega- tive	Marked acid 16 hrs	Nega- tive	Nega- tive
Park 83	Gram positive coccus, medium size, pairs and short chains, in moisture, longer chains, much vari- ation in size	Long chains	Small, smooth colony, green	Uniform cloud	Same as Park 83	Acid 21 hrs Acid and coag- ulation Partial reduc- tion 3 da	Acid	Nega- tive	Acid	Acid	Nega- tive	Nega- tive
Park-Tunnelliff	Gram positive coccus, small with pointed ends, in pairs and short chains, in moisture, much variation in size and shape, few short chains	Pairs and short chains	Small, smooth colony, green	Uniform cloud			Acid	Nega- tive	Acid	Acid	Nega- tive	Nega- tive
Tunnelliff Blood 1	Gram positive coccus, medium size, single and in groups, no chains	Definitely in pairs, no chains	Large colony smooth, white, no change in blood	Uniform cloud with stringy sediment	Slight acid No coagulation 21 hrs	Acid 21 hrs	Acid	Nega- tive	Acid	Acid	Nega- tive	Nega- tive
Throat 2	Same as Park Tunnelliff	Same as Park- Tunnelliff	Same as Park Tunnelliff	Uniform cloud	Marked acid and coagulation Reduction Color returns 21 hrs 18 hrs 5 da	Acid 21 hrs 18 hrs Reduction 5 da	Acid	Nega- tive	Acid	Acid	Nega- tive	Nega- tive
Nose 3	Gram positive coccus, small, in short chains or pairs	Very small, in clumps	Rough colony with wide, green zone	Clear with flakey sediment	Marked acid and coagulation Reduction Color returns 21 hrs 5 da	Acid 21 hrs 5 da Reduction 5 da	Acid	Nega- tive	Acid	Acid	Marked acid 16 hrs	Nega- tive
Sputum 7	Gram positive coccus, small, in pairs and chains of pairs, long chains in moisture of condensation	Very long chains	Large, smooth colony with wide green zone	Slight cloud with heavy stringy sediment	Slight acid Acid and beginning coagulation 5 da	Acid 21 hrs 5 da Reduction 5 da	Nega- tive	Nega- tive	Acid	Acid	Nega- tive	Nega- tive
Hibbard and Duval 1	Same as Park- Tunnelliff	Same as Park- Tunnelliff	Same as Park- Tunnelliff	Uniform cloud	Acid Coagulation and reduction 5 da	Acid 21 hrs 5 da Reduction 5 da	Acid	Nega- tive	Acid	Acid	Nega- tive	Nega- tive
Hibbard and Duval 2	Same as Park Tunnelliff	Same as Park- Tunnelliff	Same as Park- Tunnelliff	Uniform cloud	Marked acid and coagulation Reduction Color returns 16 hrs 18 hrs 5 da	Acid 16 hrs 18 hrs Reduction 5 da	Acid	Nega- tive	Acid	Acid	Nega- tive	Nega- tive
Hibbard and Duval 3	Same as Park- Tunnelliff	Same as Park- Tunnelliff	Same as Park- Tunnelliff	Uniform cloud	Same as Hibbard and Duval 2	Acid Same as Hibbard and Duval 2	Acid	Nega- tive	Acid	Acid	Nega- tive	Nega- tive

were made from the slant and from the moisture of condensation of the blood agar cultures, and from the broth, and stained by Gram's method

For carbohydrate fermentation, a modification of Holman's serum broth medium was employed. Horse serum was substituted for cow serum and sugar-free broth was used. As a control, each organism was grown in the same medium to which no sugar was added.

*Summary of Morphologic and Cultural Reactions*—The four Ferry cultures, *Streptococci morbilli*, are alike morphologically and culturally. They are small gram-positive streptococci, occurring in pairs and chains of pairs. They produce a small, smooth colony with a wide green zone on whole blood agar, grow in a uniform cloud in veal broth and are markedly acid with prompt coagulation and reduction in litmus milk. They ferment lactose and saccharose and are negative in mannit, salicin and inulin.

Cary 47 gives the same reactions as the Ferry cultures.

The two cultures from Park (R 83 and "Tunnichliff") are alike culturally but differ slightly morphologically, and are different from the Ferry cultures in morphology and in their fermentation of salicin.

No two of the cultures received from Tunnichliff give the same reactions. Throat 2 alone reacts similarly to Park-"Tunnichliff" and to the Hibbard and Duval cultures.

The three Hibbard and Duval cultures are much alike and agree with the Park-"Tunnichliff" and Tunnichliff-throat 2, but not with the Ferry or Cary cultures.

In addition, the bile solubility and hemolysin tests are both negative in all cultures.

#### CROSS-AGGLUTINATION REACTIONS WITH RABBIT IMMUNE SERUM

For the purpose of obtaining antisera for making serologic tests, rabbits were treated<sup>11</sup> with four Ferry cultures (01860, 01933, 01934, 01935), two nonmeasles cultures (streptococcus, nonhemolytic, 01885 and 01873), and the two cultures received from Park (83 and "Tunnichliff").

*Production of Antiserum*—In general, the method used was that given by Tunnichliff<sup>12</sup> for immunizing rabbits to the scarlatina streptococcus. She emphasized the necessity of immunizing with few and small doses to avoid polyvalency. For the first dose she used the sediment from 10 cc. of a twenty-four hour growth in ascites dextrose broth, suspended in saline and killed by heat. This was given intravenously, and after an interval of two weeks small numbers of living cocci ( $\frac{1}{8}$  blood

11 A single strain was given to each rabbit.

12 Tunnichliff, R. The Identification of the Streptococcus of Scarlet Fever, J. A. M. A. 87 625 (Aug 28) 1926.

agar slant) were injected intravenously every week or two to keep up the production of antibodies

Two rabbits each were treated with the eight cultures after tests for agglutinins were made against *Bacillus bronchisepticus*, one measles strain, 01860, and one nonmeasles streptococcus, 01873. No rabbit was used whose serum showed any degree of agglutination to these organisms in amounts less than 0.05 cc., corresponding to a dilution of 1:20.

The first dose was composed of the entire sediment from 10 cc. of an eighteen hour broth culture (0.2 per cent dextrose, Witte's peptone,  $p_H$  7.6), suspended in saline and killed by heating for thirty minutes at 56 C. The second dose, given nine days later, was 1/10 of a blood agar culture, and the third dose was 2/10 of a blood agar culture, ten days after the second dose. All injections were made intravenously.

The rabbits were sample bled and tested for agglutinins from six to eight days after each injection. The sixth day after the third injection one rabbit out of each group was bled to death. The remaining rabbits received four further doses of 1/2, 1, 2 and 3 blood agar cultures, five days apart, and were bled to death five days after the last injection. The serums were preserved with 0.2 per cent tricresol and stored at from 6 to 8 C.

There appeared to be little difference in the serums, the rabbits receiving the more injections in general produced serum of higher titer, but crossing was relatively the same.

*Agglutination Experiments*—Cross-agglutination tests were made with the eight measles and nonmeasles cultures used for the immunization of rabbits. One culture from Cary, three from Tunnichliff and three from Hibbard and Duval have been tested for agglutinins against anti-serums for Ferry and Park—"Tunnichliff" cultures. One of the cultures from Tunnichliff, nose 3, which produced a rough colony from the first, did not lend itself to agglutination. Four additional cultures of green-producing streptococci from sources other than measles were tested against anti-Ferry serum. The results of the latter experiments are taken up under agglutinin absorption experiments.

*Preparation of Suspensions*—Suspensions were prepared from the sediment from broth cultures emulsified in phosphate broth and formaldehyde. Each culture was transferred daily for several generations in veal broth (0.1 per cent dextrose,  $p_H$  8), and an eight hour growth inoculated into a flask of the same broth, incubated for from sixteen to eighteen hours, centrifugalized, and the sediment taken up in phosphate broth (1 per cent Witte's peptone, 1 per cent disodium phosphate, 0.5 per cent dextrose,  $p_H$  8) plus 0.5 per cent formaldehyde.

Suspensions for agglutination tests were diluted with phosphate broth and formaldehyde to a density corresponding to five times that of a sus-

pension of *Bacillus typhosus* containing 2,000 million organisms per cubic centimeter

*Tests*—Agglutination tests were made by a rapid method developed by one of us<sup>13</sup> (A N) 0.1 cc of heavy suspension plus 0.1 cc of diluted serum, in small test tubes, shaken slowly for two minutes, 0.5 cc of saline added and the results read

A number of tests were made using both the rapid and a standard eighteen hour method (0.5 cc of suspension plus 0.5 cc of diluted serum, in small pointed tubes, incubated eighteen hours) Suspensions for the rapid method are five times as heavy and the serum dilutions are five times as concentrated as for the slow method The results checked so closely that thereafter all tests were made by the rapid method only

TABLE 2—Agglutination Results with Measles and Nonmeasles Streptococci

Antiserum for		Highest Dilution of Serum Showing Definite Agglutination Against					
		Streptococcus morbilli				Streptococcus (Nonmeasles)	
		01860	01933	01931	01935	01873	01885
Streptococcus morbilli							
01860	Rabbit 1	1 2,000	1 2,000	1 2,000	1 2,000	1 2,000	1 2,500
	2	1 2,000	1 2,500	1 2,500	1 2,500	1 5,000	1 2,000
01933	Rabbit 3	1 2,500	1 2,500	1 2,500	1 5,000	1 2,500	1 2,500
	4	1 2,000	1 1,000	1 2,500	1 2,500	1 5,000	1 1,000
01931	Rabbit 5	1 1,000	1 1,000	1 2,000	1 1,000	1 2,500	1 2,000
	6	1 2,500	1 2,500	1 5,000	1 5,000	1 5,000	1 5,000
01935	Rabbit 9	1 2,500	1 2,000	1 2,500	1 2,500	1 5,000	1 5,000
	10	1 2,000	1 2,000	1 2,500	1 2,500	1 2,500	1 2,500
Streptococcus (nonmeasles)							
01873	Rabbit 15	1 2,000	1 2,500	1 2,500	1 2,500	1 10,000	1 2,500
	16	1 500	1 500	1 1,000	1 1,000	1 2,000	1 500
01885	Rabbit 17	1 2,000	1 1,000	1 2,000	1 2,500	1 10,000	1 10,000
	18	1 500	1 500	1 1,000	1 1,000	1 2,000	1 2,500

Table 2 shows the results of cross-agglutination tests between *Streptococcus morbilli* and two nonmeasles streptococci, table 3 gives the results with thirteen green-producing micrococci from measles, isolated by various investigators

*Summary of Agglutination Experiments*—1 Serums of high agglutinin titer were produced in rabbits by three and seven injections respectively of micrococci from measles and nonmeasles cases

2 These serums, preserved with cresol and stored in the icebox, have retained their agglutinin titers for more than one year

3 The four *Streptococcus morbilli* strains and the two nonmeasles cultures gave complete cross-agglutination reactions

4 Cary 47 was agglutinated by anti-Ferry serum but not by anti-Park-“Tunnichff” serum

13 Noble, A. A Rapid Method for the Macroscopic Agglutination Test, J Bact 14 287 (Nov) 1927

TABLE 3.—*Agglutination Results with Green-Producing Micrococci from Measles*

Antiserum for	Highest Dilution of Serum Showing Definite Agglutination Against											
	Ferry			Cary	Park			Tunncliffe			Hibbard and Duval	
	01800	01033	01031		83	Tunncliffe	Blood 1	Throat 2	Sputum 7	1	2	3
Perry	1 2,000	1 2,000	1 2,000	1 2,100	—	—	—	—	—	—	—	—
01033	1 2,500	1 2,500	1 2,500	1 2,500	—	—	—	—	—	—	—	—
01031	1 1,000	1 1,000	1 2,000	—	—	—	—	—	—	—	—	—
01035	1 2,500	1 2,000	1 2,500	—	—	—	—	—	—	—	—	—
Park	—	—	—	—	1 5,000	1 5,000	1 200	1 200	1 2,400	1 2,100	1 2,100	1 2,100
Park-Tunncliffe	—	—	—	—	1 5,000	1 5,000	1 200	1 200	1 2,400	1 2,100	1 2,100	1 2,100



5 Park 83 and Park-"Tunnichliff" cross agglutinated but did not agglutinate against Ferry serum

6 The Tunnichliff and Hibbard and Duval cultures were positive against Park-"Tunnichliff" serum and negative to Ferry serum

#### AGGLUTININ ABSORPTION REACTIONS WITH RABBIT IMMUNE SERUM

Agglutinin absorption experiments were made with the same anti-serums and cultures as those used for agglutination. Each serum was absorbed with its homologous culture and with heterologous cultures, when agglutinable, and agglutination tests were made on the resulting absorbed serums.

*Suspensions for Absorption*—These were prepared from the same emulsions as suspensions for agglutination, as follows: on the day a test was to be made a suspension was centrifugalized at high speed for

TABLE 4—Serum Dilutions

				0.1 cc
A	1:5	—	absorbed serum	= 1:50
B	1:10	—	0.4 cc A + 0.4 cc saline	= 1:100
C	1:20	—	0.2 cc A + 0.6 cc saline	= 1:200
D	1:40	—	0.1 cc A + 0.7 cc saline	= 1:400
E	1:80	—	0.1 cc B + 0.7 cc saline	= 1:800
F	1:100	—	0.1 cc B + 0.9 cc saline	= 1:1,000
G	1:200	—	0.1 cc D + 0.4 cc saline	= 1:2,000
H	1:240	—	0.1 cc D + 0.5 cc saline	= 1:2,400
I	1:500	—	0.1 cc F + 0.4 cc saline	= 1:5,000
J	1:1,000	—	0.1 cc F + 0.9 cc saline	= 1:10,000

a long period (from twenty to thirty minutes) and a 50 per cent suspension of the packed cells made in saline.

*The Absorptions*—Absorptions were also made by the rapid method: one part suspension (50 per cent cells) plus one part undiluted serum plus three parts saline, making approximately a 1:5 dilution of serum.

To a centrifuge tube (5.5 by 1.5 cm.) was added 0.3 cc of suspension, 0.3 cc of serum and 0.9 cc of saline. The tube containing the mixture was placed in a rack, the rack inclined until the tube was almost horizontal and it was then shaken slowly for ten minutes. It was centrifugalized for ten minutes, the resulting clear fluid drawn off by pipet and dilutions made as shown in table 4.

Unabsorbed serum was diluted 1:5 and the same dilutions made of it. When more than 1.2 cc of absorbed serum was needed, two tubes of the suspension-serum-saline mixture were made, as more than 1.5 cc in this size centrifuge tube does not allow for thorough mixing. The agglutination tests were carried out as before.

Table 5 gives the results of a single agglutinin absorption experiment with an antiserum for *Streptococcus morbilli*. The unabsorbed and

absorbed serum dilutions were made at the same time and in parallel. When an antistreptococcus morbilli serum was absorbed by its homologous strain, agglutinins for both the measles and nonmeasles cultures were removed. When the same serum was absorbed by a nonmeasles streptococcus, which it agglutinated, the agglutinins for that culture were removed while the measles agglutinins were but slightly reduced.

Table 6 is a summary of the agglutinin absorption results with the four strains of *Streptococcus morbilli* and two nonmeasles streptococci, table 7 gives the agglutination and agglutinin absorption results with four additional nonmeasles streptococci which culturally are identical.

TABLE 5—*Agglutinin Absorption Experiment with an Antistreptococcus Morbilli Serum*

Antiserum for S morbilli 01860 Rabbit 2	Agglutination*							
	1 50	1 100	1 200	1 400	1 800	1 1,000	1 2,000	1 2,400 Control
Before absorption against S morbilli								
01860	++++	++++	++++	++++	++++	+++	+	—
01933	++++	++++	++++	++++	++++	++++	+	—
01934	++++	++++	++++	++++	++++	+++	—	—
01935	++++	++++	++++	++++	++++	++++	+	—
Streptococcus (non measles) 01873	++++	++++	++++	++++	++++	++++	—	—
01885	++++	++++	++++	++++	++++	+++	—	—
Absorbed by S morbilli 01860 against 01860	—	—	—	—				
01933	—	—	—	—				
01934	—	—	—	—				
01935	—	—	—	—				
01873	—	—	—	—				
01885	—	—	—	—				
Absorbed by Strep- tococcus (non measles) 01885 against 01860	++++	++++	++	—	—	—	—	—
01933	++++	++++	—	—	—	—	—	—
01934	++++	++++	++	+	—	—	—	—
01935	++++	++++	++	+	—	—	—	—
01873	++++	++++	++++	++++	+	—	—	—
01885	—	—	—	—				

\* + + + +, + + +, + +, + and — mean complete, marked, partial, slight and no agglutination.

with *Streptococcus morbilli*. Table 8 gives the results with the green-producing micrococci from various workers.

*Summary of Agglutinin Absorption Experiments*—1 When a serum produced by injecting *Streptococcus morbilli* was absorbed by that culture, both specific and group agglutinins were removed (tables 5 and 6).

2 When the same serum was absorbed by a nonmeasles streptococcus, the agglutinins for that culture, group agglutinins, were removed, while the measles agglutinins, specific, were only slightly reduced (tables 5, 6 and 7).

3 The four *Streptococcus morbilli* strains appeared to be similar by agglutinin absorption.

(a) When an antiserum for 01860 was absorbed by 01933, 01934 or 01935, the agglutinins for 01860 were greatly reduced.

TABLE 6—*Agglutinin Absorption Results with Measles and Nonmeasles Streptococci*

Antiserum for		Highest Dilution of Serum Showing Definite Agglutination Against					
		Streptococcus morbilli				Streptococcus (Nonmeasles)	
		01860	01933	01934	01935	01873	01885
S morbilli 01860	Rabbit 1						
Before absorption		1 2,000	1 2,000		1 2,000	1 2,400	1 2,000
Absorbed by S morbilli 01860		—	—		—	—	—
S (nonmeasles) 01873		1 1,000	1 400		1 1,000	—	1 800
	Rabbit 2						
Before absorption		1 2,000	1 2,000	1 1,000	1 2,000	1 1,000	1 1,000
Absorbed by S morbilli 01860		—	—	—	—	—	—
	01933	—	—	—	—	—	—
	01934	—	—	—	—	—	—
	01935	1 100	1 100	1 100	1 100	—	—
S (nonmeasles) 01885		1 200	1 100	1 400	1 400	1 800	—
S morbilli 01933	Rabbit 3						
Before absorption		1 2,400	1 2,400	1 2,400	1 2,400	1 2,400	1 2,400
Absorbed by S morbilli 01933		—	—	—	—	—	—
	01860	1 200	1 400	1 400	1 400	—	—
S (nonmeasles) 01885		1 1,000	1 1,000			1 400	—
	Rabbit 4						
Before absorption		1 2,000	1 2,000			1 5,000	1 1,000
Absorbed by S morbilli 01933		—	—			—	—
S (nonmeasles) 01885		1 1,000	1 1,000			1 400	—
S morbilli 01934	Rabbit 5						
Before absorption		1 1,000		1 2,000		1 2,400	1 1,000
Absorbed by S morbilli 01934		—		—		—	—
S (nonmeasles) 01885		1 200		1 400		1 400	—
	Rabbit 6						
Before absorption		1 5,000	1 5,000	1 5,000	1 5,000	1 5,000	1 5,000
Absorbed by S morbilli 01934		—	—	—	—	—	—
	01860	—	1 100	1 100	1 100	—	—
S (nonmeasles) 01885		1 1,000		1 2,000		1 2,000	—
S morbilli 01935	Rabbit 9						
Before absorption		1 2,400	1 2,400	1 2,400	1 2,400	1 5,000	1 5,000
Absorbed by S morbilli 01935		—	—	—	—	1 50	—
	01860	—	—	1 50	1 50	—	—
S (nonmeasles) 01885		1 800			1 1,000	1 2,000	—
	Rabbit 10						
Before absorption		1 2,000			1 2,400	1 2,400	1 2,400
Absorbed by S morbilli 01935		—			—	1 50	—
S (nonmeasles) 01885		1 400			1 400	1 400	—
S (nonmeasles) 01873	Rabbit 15						
Before absorption		1 800	1 2,400			1 10,000	1 2,000
Absorbed by S (nonmeasles) 01873		—	—			1 50	—
S morbilli 01860		—	—			1 1,000	1 100
	Rabbit 16						
Before absorption		1 200	1 400			1 2,000	1 400
Absorbed by S (nonmeasles) 01873		—	—			—	—
S morbilli 01860		—	—			1 200	—
S (nonmeasles) 01885	Rabbit 17						
Before absorption		1 2,500	1 1,000	1 2,000	1 2,400	1 5,000	1 10,000
Absorbed by S (nonmeasles) 01885		1 100	—	—	—	1 50	1 200
S morbilli 01860		1 50	—	—	1 100	1 400	1 1,000
	Rabbit 18						
Before absorption		1 800	1 1,000	1 1,000	1 1,000	1 2,000	1 2,400
Absorbed by S (nonmeasles) 01885		—	—	—	—	—	—
S morbilli 01860		—	—	—	—	—	1 1,000

(b) And, conversely, when an antiserum for 01933, 01934, or 01935 was absorbed by 01860, the agglutinins for 01933, 01934 and 01935 were greatly reduced (table 6)

(c) Also, the agglutinins for all were absorbed from an antistreptococcus morbilli serum by any one strain of *Streptococcus morbilli*

4 Two nonmeasles cultures of green-producing streptococci, 01873 and 01885, while agglutinating antiserum for *Streptococcus morbilli* to titer, were distinguished from *Streptococcus morbilli* by absorption

(a) When an antiserum for *Streptococcus morbilli* was absorbed with nonmeasles streptococcus, the agglutinins for *Streptococcus morbilli* were only slightly reduced (tables 5 and 6)

TABLE 7—*Agglutination and Agglutinin Absorption Results with Nonmeasles Streptococci*

Antiserum for S morbilli 01860 Rabbit 2	Agglutination							
	1 50	1 100	1 200	1 400	1 800	1 1,000	1 2,000	Controls
Before absorption against S morbilli 01860	++++	++++	++++	++++	++++	+++	+	—
Streptococcus (nonmeasles)								
01890	—	—	—	—	—	—	—	—
01966	++++	++++	++++	+++	++	+	—	—
01983	++++	++++	++++	+++	—	—	—	—
01987	++++	++++	++++	+++	—	—	—	—
Absorbed by 01966								
Against 01966	—	—	—	—				
01860	++++	++++	++++	+++	+	—	—	
Absorbed by 01983								
Against 01983	—	—	—	—				
01860	++++	++++	++++	++++	++	+	—	
Absorbed by 01987								
Against 01987	—	—	—	—				
01860	++++	++++	++++	++++	+++	+	—	

(b) And, conversely, when an antiserum for a nonmeasles culture was absorbed with *Streptococcus morbilli*, the agglutinins for the nonmeasles culture were only slightly reduced (table 6)

5 Three nonmeasles cultures, 01966, 01983 and 01987, are presumptively different from *Streptococcus morbilli* as no one of them absorbs agglutinins for 01860 from an 01860 serum (table 7)

6 Cary 47 and the Ferry cultures are presumptively similar When a Ferry serum was absorbed by Cary 47, the agglutinins for each culture were removed (table 8)

7 The two cultures received from Park appear to be similar (table 8)

(a) When an antiserum for Park 83 was absorbed by Park-“Tunnichliff,” agglutinins for Park 83 were greatly reduced

(b) And, conversely, when an antiserum for Park-“Tunnichliff” was absorbed by Park 83, agglutinins for Park-“Tunnichliff” were greatly reduced

TABLE 8.—Agglutination Results with Green-Producing Micrococci from Measles

Antiserum for	Highest Dilution of Serum Showing Definite Agglutination Against									
	Ferry			Coley			Park			Hibbard and Duval
	01860	01933	01934	01935	17	83	Tunnell's Blood 1	Tunnell's Throat 2	Sputum 7	
Lerry 01860	1 2 000	1 1,000	1 2,000	1 2 000	1 2,400	—	—	—	—	—
Before absorption	—	—	—	—	—	—	—	—	—	—
Absorbed by Lerry 01860	—	—	—	—	—	—	—	—	—	—
01933	—	—	—	—	—	—	—	—	—	—
01934	—	—	—	—	—	—	—	—	—	—
01935	1 100	1 100	1 100	1 100	—	—	—	—	—	—
Coley 17	—	—	—	—	—	—	—	—	—	—
Park 83	—	—	—	—	—	1 5,000	1 5,000	—	—	—
Before absorption	—	—	—	—	—	—	—	—	—	—
Absorbed by Park 83	—	—	—	—	—	1 100	—	—	—	—
Park Tunnell's	—	—	—	—	—	—	—	—	—	—
Before absorption	—	—	—	—	—	1 5,000	1 5,000	1 200	1 2,400	1 2,400
Absorbed by Park-Tunnell's	—	—	—	—	—	—	—	—	—	—
Park 83	—	—	—	—	—	—	1 100	—	—	—
Tunnell's, blood 1	—	—	—	—	—	—	1 5,000	—	—	—
Tunnell's, throat 2	—	—	—	—	—	—	—	—	—	—
Tunnell's, sputum 7	—	—	—	—	—	—	—	—	—	—
Duval 3	—	—	—	—	—	—	1 2,400	—	—	—

8 Tunnichff-throat 2 is presumptively similar to Park-“Tunnichff,” as it absorbed agglutinins for that culture (table 8)

9 Tunnichff-blood 1 and sputum 2, while agglutinating in Park-“Tunnichff” serum, did not absorb agglutinin for Park-“Tunnichff”

10 The three Hibbard and Duval cultures are presumptively alike and similar to Park-“Tunnichff” When Park-“Tunnichff” serum was absorbed by Hibbard and Duval 3, agglutinins for Hibbard and Duval 1, 2 and 3 and for Park-“Tunnichff” were greatly reduced (table 8)

#### COMPLEMENT-FIXATION REACTIONS WITH RABBIT IMMUNE SERUM

Homologous and cross-complement-fixation tests were made with the same serums and cultures as those used for agglutination

*Preparation of Antigens for Complement-Fixation Tests*—Antigens were prepared by a modification of the Wilson and McNeil method for defatted gonococcus antigens<sup>14</sup>

Each culture was grown for twenty-four hours on 0.2 per cent dextrose-ascitic agar in Roux flasks of 1 quart capacity, the growth washed off in 15 cc of saline and made up to 50 cc per flask. Each suspension was shaken for fifteen minutes in a mechanical shaker, then centrifugalized and the supernatant fluid poured off.

To the sediment from ten flasks in a centrifuge tube was added 50 cc of absolute alcohol. This mixture was heated in a water-bath at 56 C for thirty minutes, and was stirred constantly with a glass rod. It was then centrifugalized for ten minutes and the alcohol discarded. To the residue, 50 cc of Squibb's ether was added and stirred constantly for thirty minutes at room temperature, again centrifugalized, the ether discarded and the sediment allowed to dry at room temperature. When thoroughly dry and free from the odor of ether, the powder was triturated in distilled water plus 0.5 per cent of phenol in the proportion of 1 Gm in 200 cc. These bacterial suspensions were then autoclaved for twenty minutes at a pressure of 15 pounds.

Satisfactory and stable antigens of the sixteen cultures have been prepared by this method. They are not hemolytic in doses of 0.5 cc of a 1:5 dilution, but they are slightly anticomplementary, and the antigenic units range from 0.5 cc of 1:100 to 0.5 cc of 1:1,000.

*The Test*—The complement-fixation tests were made by an adaptation of the new Kolmer method<sup>15</sup> for syphilis.

Amboceptor and complement were titrated daily. Four units of antigen (01860) were used in the complement titration. The serum from

14 Park, W. H., and Williams, A. W. Pathogenic Microorganisms, ed. 8, Philadelphia, Lea & Febiger, 1924, pp. 258 and 273.

15 Kolmer, J. A. Infection, Immunity and Biologic Therapy, ed. 3, Philadelphia, W. B. Saunders Company, 1924, p. 478.

not less than three guinea-pigs was pooled for complement. The fixation period was eighteen hours at from 6 to 8 C.

The dose of antigen was from two to four times the antigenic unit, in most cases four times, depending on the anticomplementary unit. Antigens, for which we had no homologous antiserum, were used in doses of one-fourth the anticomplementary unit.

The serum dilutions were from 1/20 to 1/1,250. The dose was 0.5 cc of these, making the final dilutions 1/40 to 1/2,500, the same dilutions as used for the straight agglutination tests. A few of the serums were anticomplementary, but the serum from at least one rabbit on each organism could be utilized.

Tables 9 and 10 give the results of the complement-fixation tests.

*Summary of the Complement-Fixation Experiments*—1 The four strains of *Streptococcus morbilli* and the two nonmeasles streptococci showed cross fixation to titer (table 9).

TABLE 9—*Complement-Fixation Results with Measles and Nonmeasles Streptococci*

Antiserum for		Highest Dilution of Serum Showing Definite Fixation Against Antigens of					
		Streptococcus morbilli				Streptococcus (Nonmeasles)	
		01860	01933	01934	01935	01873	01885
Streptococcus morbilli							
01860	Rabbit 1	1/1,000	1/1,000	1/2,000	1/1,000	1/1,000	1/1,000
	Rabbit 2	1/500	1/500	1/1,000	1/400	1/500	1/500
01933	Rabbit 4	1/500	1/400	1/1,000	1/500	1/100	1/100
01934	Rabbit 5	1/1,000	1/1,000	1/2,000	1/1,000	1/500	1/500
01935	Rabbit 10	1/500	1/500	1/1,000	1/500	1/400	1/500
Streptococcus (nonmeasles)							
01873	Rabbit 15	1/2,500	1/2,500	1/2,500	1/2,500	1/2,500	1/2,500
01885	Rabbit 18	1/1,000	1/500	1/1,000	1/400	1/400	1/500

2 Ferry 01860 did not cross with Park 83 or Park-"Tunnichiff" serum (table 10).

3 Cary 47 showed marked fixation against antistreptococcus morbilli serum only.

4 Park 83, Park-"Tunnichiff," Tunnichiff-throat 2, and the three Hibbard and Duval cultures showed fixation with Park 83 and Park-"Tunnichiff" serum and were negative to Ferry serum.

5 Tunnichiff strains, blood 1, nose 3 and sputum 7 were negative to both Ferry and to Park-"Tunnichiff" serum.

#### AGGLUTINATION AND COMPLEMENT-FIXATION TESTS WITH MEASLES CONVALESCENT SERUM

The serum was furnished by Dr. Fred M. Meader of the Detroit Board of Health, from patients whose histories were verified by the physician who attended them during their attack of measles. All the serums

TABLE 10.—Complement-Fixation Results with Green-Producing *Micrococci* from Measles

Antiserum for	Highest Dilution of Serum Showing Definite Fixation Against Antigens of																									
	Ferry				Cary		Park		Tunnichiff				Hibbard and Duval													
	01860		01933		01934		01935		47		S3		Tunnichiff		Blood 1		Throat 2		Nose 3 Sputum 7		1		2		3	
Ferry 01860	1	1,000	1	1,000	1	2,000	1	1,000	1	500	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
01933	1	500	1	400	1	1,000	1	500	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
01934	1	1,000	1	1,000	1	2,000	1	1,000	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
01935	1	500	1	500	1	1,000	1	500	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
Park S3	1	40	—	—	—	—	—	—	1	40	1	500	1	500	—	—	1	500	—	—	—	—	—	—	—	
Park-Tunnichiff	1	80	—	—	—	—	—	—	1	80	1	500	1	500	1	80	1	500	—	—	—	—	—	—	—	



were preserved with tricresol and were filtered clear immediately before using. This serum was being employed by the Detroit Board of Health for prophylactic purposes. One hundred and fifty-one serums have been studied, but, as many of these were repeated bleedings, results with the first bleedings only are considered in this report.

Serums from eighty-three patients convalescent from measles were tested for agglutinins for Ferry 01860, Cary 47, Park-"Tunnichliff" and Hibbard and Duval 3, and thirty-nine were tested for complement-fixation against antigens of the same organisms. These four cultures were chosen because they seemed to be the most representative of the two predominating groups among the micrococci studied.

TABLE 11—*Agglutination and Complement-Fixation Results with Measles Convalescent Serums*\*

Serum Num ber	Age of Patient When Bled Years	Time Since Patient Had Measles	Agglutination Reaction				Complement Fixation			
			Ferry 01860	Cary 47	Park- Tunni- chiff	Hibbard and Duval	Ferry 01860	Cary 47	Park Tunni- chiff	Hibbard and Duval
2	27	5 mos	4 3 3 2	4 4 3 -	—	—	A C †	—	—	—
3	34	1½ mos	3 4 4 2	4 4 4 4	1 - -	1 - -	A C	—	—	—
4	28	2 mos	4 3	4 4	—	—	3 2 1 -	2 1 1 -	—	2 1 - -
5	15	2¼ mos	3 1 - -	4 2 1 -	—	—	4 3 2 1	4 3 2 -	—	3 2 1 -
6	15	2½ yrs	1 - - -	2 1 - -	—	—	A C	—	—	—
7	26	1 mo	4 3 2 1	4 3 - -	—	—	A C	—	—	—
11	15	2 mos	2 1 - -	2 1 - -	—	—	2 1 - -	2 1 - -	—	—
12	11	2 mos	3 4 1 -	3 1 - -	—	2 1	A C	—	—	—
14	19	2 mos	3 1 - -	4 3 - -	—	2 - -	3 2	3 2	—	—
15	24	3 mos	3 2 1 -	3 2 1 -	—	—	2 1 - -	2 1 - -	—	1 - - -
16	12	15 days	4 4 1 -	4 4 1 -	—	—	2 1 - -	2 1 - -	—	1 - -
17	22	3 mos	—	—	—	—	A C	—	—	—
19	21	11 mos	4 2 1 -	4 3 - -	—	—	4 3 1 -	4 4 1 -	4 1 - -	4 3 - -
20	30	18 days	3 2 - -	4 4 4 -	—	—	3 1 - -	3 1 - -	1 - - -	2 - - -
21	17	10 mos	3 2 1 -	2 1 - -	—	—	3 2 1 -	2 1 1 -	—	—
22	26	3 wks	4 4 3 2	4 4 4 4	1 - -	—	A C	—	—	—
25	23	2 mos	2 1 - -	1 - - -	1 - -	—	1 1 - -	1 1 - -	—	—
33	23	2 yrs	4 4 4 1	4 4 4 3	—	—	4 4	4 3	4 -	4 -
41	31	3¼ yrs	2 1 - -	3 3 1 -	—	4 - -	3 2 1 -	3 2 1 -	1 - - -	1 - - -
43	40	10 mos	2 1 - -	2 1 - -	—	—	—	—	—	—
44	16	10 mos	2 2 1 -	3 1 - -	—	—	—	—	—	—
49	14	1 mo	—	1 - - -	—	—	—	—	—	—
51	13	1 mo	—	4 3 - -	—	—	—	1 - - -	3 2 - -	2 1 - -
52	15	12 mos	2 - - -	4 3 - -	—	—	1 - - -	1 - - -	—	—
53	23	1 yr	—	—	—	—	1 - - -	1 - - -	—	—

\* Serum amounts used in agglutination and complement fixation tests were 0.1, 0.05, 0.025 and 0.01 cc. 4, 3, 2, 1, - mean the complete, marked, partial, slight and no agglutination, or complement fixation.

† A C = anticomplementary.

Agglutination tests were made by the rapid method, undiluted serum being used in amounts of 0.1, 0.05, 0.025 and 0.01 cc delivered with a 0.1 or 0.2 cc pipet to the bottom of the tubes. A preliminary reading was made immediately after the two minute shaking period and the addition of 0.5 cc of saline, and the tests were allowed to stand at room temperature overnight, when the final reading was made. Reactions with serums of such low titer are easier to read after standing for a few hours.

Complement-fixation tests were made by the new Kolmer method, the same amounts of serum were used made up to 0.5 cc with saline.

Table 11 gives the results with serum from the first twenty-five patients, on whom both tests were made, together with the age of the

patient and the length of time since the patient had measles Table 12 gives a summary of the agglutination and complement-fixation results

In addition to these, serums from sixteen patients who had had measles not more than two months prior to bleeding were tested for agglutinins against all thirteen measles cultures being studied

*Summary of Agglutination and Complement-Fixation Experiments*—Considering the eighty-three serums tested against the four cultures, 86.7 per cent agglutinated the Ferry culture, 90.3 per cent Cary 47, 84 per cent Park-“Tunnichiff” and 96 per cent the Hibbard and Duval culture 3. The Ferry and Cary cultures often showed marked agglutination in all four amounts, while the Park-“Tunnichiff” and Duval culture seldom showed more than 2+ agglutination in the largest amount (0.1 cc)

Of the convalescent serums on which complement-fixation tests were made, twelve were anticomplementary, and of the remaining twenty-

TABLE 12—*Summary of Results with Measles Convalescent Serum*

	Agglutination				Complement Fixation			
	Total Tested	Reaction		Per Cent +	Total Tested	Reaction		Per Cent +
		+	—			+	—	
Ferry 01860	83	72	11	86.7	27	21	6	78
Cary 47	83	75	8	90.3	27	21	6	78
Park-Tunnichiff	83	7	76	8.4	27	9	18	33
Hibbard and Duval 3	83	8	72	9.6	27	13	14	48

seven, 78 per cent showed fixation with both Ferry and Cary cultures, 33 per cent with Park-“Tunnichiff” and 48 per cent with the Duval culture

Of the sixteen serums from recent cases tested against thirteen suspensions, all agglutinated the four Ferry strains and Cary 47. One serum was positive to all cultures. Thirteen were negative to Park-“Tunnichiff,” Tunnichiff-throat 2 and the three Duval cultures. Nine were positive to Tunnichiff-blood 1 and fourteen were positive to Tunnichiff-sputum 7.

#### AGGLUTININ ABSORPTION REACTIONS WITH MEASLES CONVALESCENT SERUM

Owing to the fact that fourteen of the sixteen serums from recent cases of measles agglutinated Tunnichiff's culture sputum 7, it was decided to try absorption tests with such serums. As the nonmeasles culture 01885 crossed so completely with *Streptococcus morbilli* serum, this organism also was included.

A number of serums from recent cases were tested for agglutinins against these two cultures in addition to Ferry 01860, Cary 47, Park-

"Tunnichliff" and Duval 3, and the five serums giving the highest titers were selected for absorption reactions

Each serum was absorbed by Ferry 01860, Tunnichliff-sputum 7 and streptococcus (nonhemolytic) 01885, and the resulting absorbed serums were tested for agglutinins against the same three suspensions and Cary 47

For absorption, equal parts of serum and suspension (25 per cent packed cells) were shaken slowly in a centrifuge tube for ten minutes, centrifugalized for ten minutes and serum removed. The absorbed serum was considered as a dilution of 1/2, though actually it is not diluted that much because of the space occupied by the bacteria in the

TABLE 13—*Agglutinin Absorption Experiment with a Convalescent Serum*

Convalescent Serum 146	Agglutination					Control
	1/10	1/20	1/40	1/80	1/100	
Before absorption against						
Ferry 01860	++++	++++	+++	++	+	—
Cary 47	++++	++++	+++	++	+	—
Park Tunnichliff	—	—	—	—	—	—
Duval 3	—	—	—	—	—	—
Tunnichliff, sputum 7	++++	+++	—	—	—	—
Streptococcus 01885	++++	++++	++++	++++	+++	—
Absorbed by Ferry 01860 against						
Ferry 01860	—	—	—	—	—	—
Cary 47	—	—	—	—	—	—
Sputum 7	++	+	—	—	—	—
Streptococcus 01885	++	+	—	—	—	—
Absorbed by sputum 7 against						
Ferry 01860	+++	++	+	+	—	—
Sputum 7	—	—	—	—	—	—
Streptococcus 01885	++++	++++	++++	+++	—	—
Absorbed by Streptococcus 01885 against						
Ferry 01860	++	+	+	+	—	—
Cary 47	+++	++	++	+	—	—
Sputum 7	++++	+++	—	—	—	—
Streptococcus 01885	—	—	—	—	—	—

25 per cent suspension. This error, however, is in the right direction as it makes the test for absorption that much more rigid.

The unabsorbed serum was diluted 1/2 with saline and each tested for agglutinins in amounts of 0.2, 0.1, 0.025 and 0.02 cc., corresponding to dilutions of 1/10, 1/20, 1/40, 1/80 and 1/100.

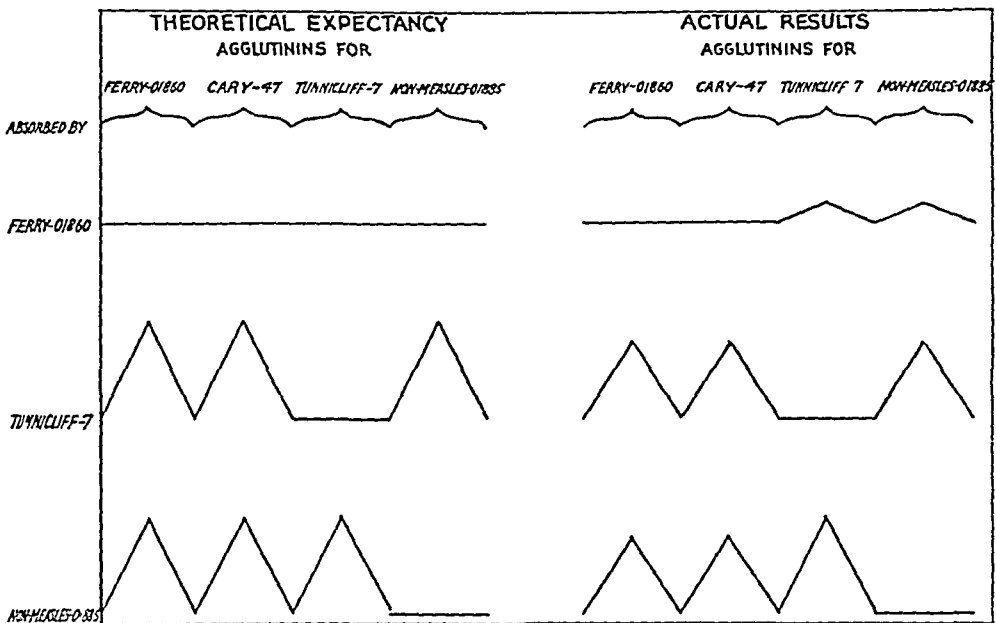
In table 13 are given the results with one of the serums, which is typical of the five tested.

*Summary and Discussion of Agglutinin Absorption Experiments*—Ferry 01860 absorbed the agglutinins for Ferry 01860 and Cary 47, and almost completely absorbed the agglutinins for Tunnichliff 7 and non-measles streptococcus 01885.

Tunnichliff 7 removed the agglutinins for Tunnichliff 7 and slightly or not at all reduced the agglutinins for 01860, 47 and 01885.

Nonmeasles streptococcus 01885 removed the agglutinins for 01885, slightly reduced the agglutinins for 01860 and 47 and generally left them intact for Tunnichliff 7.

Assuming that the agglutinin-absorption test can be relied on for determining specificity and assuming also that the agglutinins found in the majority of the measles convalescent serums for Ferry 01860, Cary 47, Tunnichiff 7 and nonmeasles streptococcus 01885 are specific for Ferry 01860 and Cary 47 and are nonspecific or group agglutinins for the other two organisms, the theoretical conditions would be as follows Ferry 01860 and Cary 47 would completely absorb the agglutinins for Ferry 01860, Cary 47, Tunnichiff 7, and nonmeasles 01885, Tunnichiff 7 would completely absorb agglutinins for 7 but not for 01860, 47 and 01885, and 01885 would completely absorb agglutinins for 01885 and not for 01860, 47 and 7



Results with agglutinin absorption experiment with measles convalescent serums

As a matter of fact, the actual results approached closely the theoretical expectancy, as may be seen in table 13 and also in the accompanying chart, in which the results are shown graphically

In the chart, the bottom of the curve, or the horizontal line, represents complete absorption, while the tip of the curve represents the limits of the agglutination titers

#### SUMMARY AND COMMENT

From the results of this work it seems apparent that the green-producing micrococci, described by the several authors quoted, are not similar

Morphologically, culturally and serologically *Streptococcus morbilli* strains are identical

Cary 47 agrees in every respect with *Streptococcus morbilli*

The two cultures from Park, designated as R 83 and "Tunnichliff," are essentially alike

The three cultures from Hibbard and Duval are alike and agree with the two Park cultures

No two of the strains received from Tunnichliff are alike

Throat 2 from Tunnichliff agrees with the Park cultures and the three Hibbard and Duval cultures

When the straight agglutination test does not differentiate these green-producing micrococci, the agglutinin-absorption test can be relied on

Complement-fixation results run about parallel with the straight agglutination results and are no more specific

Of eighty-three measles convalescent serums studied, the large majority (88.5 per cent) agglutinated the Ferry and Cary cultures, while only a small proportion (9 per cent) showed any degree of agglutination with the Park-"Tunnichliff" and Hibbard and Duval cultures, and these only in the lowest dilutions of the serum tested

Evidence, therefore, has hereby been produced, contrary to some opinions previously expressed in the literature, to the effect that the various green-producing micrococci obtained from measles included in this study are not all similar, in fact, there is such a wide variation between some of them that they do not compare morphologically, culturally or serologically

It is apparent also that if all of these organisms sponsored by the several authors mentioned in this paper, are related to measles, in an etiologic capacity, it must be as a more or less heterogeneous group composed of several distinct types

## Book Reviews

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UEBER DAS PROBLEM DER BOSARTIGEN GESCHWULSTE — EINE EXPERIMENTELLE UND THEORETISCHE UNTERSUCHUNG VON PROF DR LOTHAR HEIDENHAIN Paper Price, 28 marks Pp 153, with 141 illustrations Berlin Julius Springer, 1928

The author's working hypothesis that malignant tumors arise from an infectious origin was developed during forty years of surgical experience. During the past four years he has submitted it to an experimental analysis. About 2,400 white mice received injections of autolysates of certain closed carcinomas and sarcomas of human origin. The methods used in preparing the autolysates and making the injections are fully given. A 10 per cent suspension of fresh tumor substance in normal physiologic sodium chloride solution was also inoculated. Certain of the mice likewise were inoculated with tumors of animal origin. About 6 or 7 per cent of the inoculated mice developed neoplasms, which were studied.

The extensive experimental work is carefully and rather completely presented. It is splendidly illustrated, the numerous figures themselves are a real contribution to the study of cancer.

There cannot be any doubt that the tumors are real neoplasms. Heidenhain concludes that white mice may be successfully inoculated with various autolysates of human and animal carcinomas and sarcomas. A considerable number of the mice developed sarcomas after inoculation with carcinomatous autolysate and vice versa. As a consequence, the author concludes that the actuating influence, the "Erreger" or "Agens," is the same for both carcinoma and sarcoma. The neoplasms do not develop at the site of inoculation but in some distant region. Clinically and pathologically, they are essentially similar to those in man. Thus in spite of the position taken by most pathologists, particularly that adopted at the meeting of the German Pathological Society in 1926, the author remains an ardent advocate of the theory of infection.

Of major importance in the evaluation of results secured by Heidenhain is the question of the origin of spontaneous tumors in white mice. The tumors reported appeared in from three and one-half months to twenty-five months, usually about a year after the inoculation. The results would be more convincing had the tumors appeared in cancer-free strains such as those developed by Maude Slye. Differences in interpretation of the thoroughly presented data, however, do not detract from the general excellence of the monograph, which should prove of especial interest and value to students of cancer research.

MEDICINE MONOGRAPHS, VOLUME XIV EPILEPSY By WILLIAM G LENNOX, Assistant in Medicine, Research Fellow in Neuropathology, Harvard Medical School and STANLEY COBB BULLARD, Professor of Neuropathology, Harvard Medical School Price, \$3.50 Pp 197 Baltimore Wilkins & Wilkins Company, 1928

This monograph, dedicated to William N Bullard, is not an ordinary treatise on the "disease" epilepsy, but a comprehensive analytic study of the factors involved in convulsions in general. In fact, the authors maintain that our knowledge does not permit us to designate any convulsive state as "idiopathic" or "essential" epilepsy. There is no constant anatomic lesion in epilepsy, and only a minority of patients with extensive cerebral pathologic changes have fits. The authors accept the evidence adduced in favor of vasomotor control of the cerebral vessels as conclusive and lay some stress on signs of instability of the sympathetic nervous system in epilepsy. They hail as the greatest recent advance the demonstration that changes in physiochemical processes may modify seizures.

profoundly Paraphrasing the famous statement of Hippocrates that anyone who can render a man humid and dry, and hot and cold by regimen can cure epilepsy, they say "Whoever is acquainted with physiology and can render a man acidotic, dehydrated and fully oxygenated can also repress this disease, without minding purification of narcissistic personalities, ritualistic imperial diets and all other illiberal practices of a like kind" Alkalosis and anoxemia are considered of importance as convulsive factors, while acidosis often is beneficial whether induced by rebreathing, ketosis or the administration of acids or acid-forming salts Any person interested in scientific medicine will enjoy this book

MODERN MEDICINE ITS THEORY AND PRACTICE VOLUME VI DISEASES OF THE NERVOUS SYSTEMS, AND DISEASES AND ABNORMALITIES OF THE MIND Original Contributions By American and Foreign Authors Edited by Sir William Osler, Bart, M D, F R S, Late Regius Professor of Medicine in Oxford University Third Edition Reedited by Thomas McCrae, M D, Professor of Medicine in the Jefferson Medical College, Assisted by Elmer H Funk, M D, Clinical Professor of Medicine, Jefferson Medical College Price, \$54 a set, \$9 a copy Philadelphia Lea & Febiger, 1928

The sixth and last volume of the revised edition of Osler's "Modern Medicine" is devoted to diseases of the nervous system and abnormalities of the mind The twenty-one contributors include men who are well known in the field of Medicine in both America and England, and each of whom is an authority on his subject Among these are Lewellys, F Barker, Joseph Collins, Harvey Cushing and J Ramsay Hunt The introductory chapter on diseases of the nervous system by Barker should prove valuable to the general practitioner He discusses the symptoms and physical observations of nervous disorders in general, discussing the physiologic background and diagnostic significance of such phenomena Thereafter each of the major diseases of the nervous system is analyzed completely and authoritatively by the various contributors The part by Edward A Strecker, devoted to the diseases and abnormalities of the mind, emphasizes the importance of psychiatry in general medicine He simplifies existing classifications and points out the significant manifestations presented by patients, in such a manner as to make them readily understandable to others than specialists in this field On the whole, the third edition of this work succeeds in keeping Osler's Modern Medicine in the front rank of systems in medicine

SYPHILIS, A TREATISE ON ETIOLOGY, PATHOLOGY, SYMPTOMATOLOGY, DIAGNOSIS, PROPHYLAXIS AND TREATMENT By HENRY H HAZEN Price, \$4 Pp 643, with 165 illustrations, including 16 figures in color St Louis C V Mosby Company, 1928

This conveniently sized work contains an amazing amount of material, and presents concisely every aspect of syphilis It tends to be a compilation, and other authors have written a few chapters The text is well illustrated by photographs, photomicrographs and colored plates Many of the legends preach unforgettable sermons

The text is valuable in enabling students and practitioners to obtain a bird's-eye view of the disease and become familiar with general principles The most valuable feature is that of diagnosis, which is incorporated throughout the early chapters and not confined to the one so designated Syphilis in the negro is discussed

The size of the text would permit, and its value would be enhanced by inclusion of more of the refinements of syphilologic practice Individualization of patients for treatment and more detailed study of contraindications to and complications of therapy are of such great practical importance that more space could be devoted to them

**METABOLISME CELLULAIRE ET METABOLISME DES TUMEURS** OTTO WARBURG  
Translated by E Aubel and L Genevois Price, 30 francs Paris Félix  
Alcan, 1928

This is not an exact translation of Warburg's "Stoffwechsel der Tumoren" published in Berlin in 1926, but it includes some of his more recent publications, and thus brings his work in its most recent state before the French-reading public. On the whole, the work is highly technical, dealing with the methods used by Warburg in his work on the metabolism of tissues, and with the results obtained by the study of various tissues, especially cancer tissue. The work, thus, is of interest chiefly to the biologist interested in the fundamental problems of the oxidation of tissues, and to the investigator in the field of cancer.

Two chapters of more general interest incorporated within the present volumes are "The Metabolism of the Cancer Cell" and "The Present State of the Problem of Cancer." As Warburg's epoch-making work is not yet available in English, this translation may bring his methods, results, conclusions and speculations within the reach of a new group of readers.

**EPILEPSY** By WILLIAM G LENNOX, Assistant in Medicine, Harvard Medical School, and STANLEY COBB, Bullard Professor of Neuropathology, Harvard Medical School. Medicine Monographs, Volume XIV. Cloth Price, \$3.50. Pp 197, with 14 illustrations. Baltimore: Williams & Wilkins Company, 1928.

This is a valuable and fascinating study of the factors involved in convulsions in general. The authors, who have done important investigative work in this field, also prove themselves equipped with a thorough grasp of old and recent research work in physiology, chemistry and pathology which has a bearing on this problem. While cautious in drawing conclusions and not at all ready to offer a solution to the riddle of epilepsy, they lay greater emphasis on chemical factors, such as alkalosis and "oxygen lack," and on disordered sympathetic nerve function and arterial spasm, than on the meager and inconstant information given by microscopic examination. Their reasoning leads them to discard the distinction between "idiopathic" and "symptomatic" epilepsy, as this implies a knowledge which we do not possess. However, they sound this hopeful note: "The encouraging feature is that, although the exact mechanism of seizures is unknown, much can be done to prevent and, in the early stages, to cure them. It is the duty of the physician to search out the various contributing or precipitating factors which, in the individual patient, may make for seizures. Correction of these abnormalities may effect sympathetic cure." The book can be highly recommended to the general medical reader as one that deals with a difficult subject in a clear, orderly and interesting manner.

**CUSHNY'S PHARMACOLOGY AND THERAPEUTICS** By C W EDMUNDS, University of Michigan, and J A GUNN, University of Oxford. Ninth edition, revised. Cloth Price, \$6. Pp 743. Philadelphia: Lea & Febiger, 1928.

Probably no textbook has played as important a part in the recognition and development of pharmacology in this country as has Cushny's. Workers in this field and in therapeutics will therefore welcome this latest edition, which has been revised and brought up to date by Edmunds and Gunn.

The general plan of the work has not been at all altered. The chief changes in the new edition are the insertion of the drug descriptions and dosages of the tenth United States Pharmacopeia, and alterations or extensions of the text to conform with progress in pharmacology and therapeutics. These changes have lengthened the book about thirty-six pages.



THE EXAMINATION OF PATIENTS By NELLIS B FOSTER, M.D., Associate Physician to the New York Hospital, Associate Professor of Medicine at Cornell University College of Medicine Second edition, revised Price, \$4.50 Pp 371, with numerous charts, plates and index Philadelphia W B Saunders Company, 1928

In revising this well known book for its second edition the author has dealt briefly with the differential diagnosis of the more important diseases Paragraphs on symptomatology are appropriately interspersed with those on systematic or regional examination A whole chapter on the febrile diseases has been added The diagnostic laboratory procedures have been brought up to date

For a small manual it contains a wealth of valuable information and could profitably be kept on the study table of every senior student and intern

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## PEPTIC ULCER

THE EFFECT OF PARENTERAL INJECTIONS OF PURIFIED MILK  
PROTEINS ON THE SYMPTOMS AND PROGRESS \*

LAY MARTIN, M D

BALTIMORE

This paper appears only as a preliminary report. The results of the study have been so interesting and some of them so conclusive that I could not resist presenting the matter at the present time.

By peptic ulcers I mean those on both sides of the pylorus.

As far as I can discover, the first voluntary administration of foreign protein in the treatment for peptic ulcer was Gottfried Holler,<sup>1</sup> who reported on the matter in 1921.

In 1922, Pribram,<sup>2</sup> a surgeon in Bier's Clinic, published his reports on the treatment for peptic ulcers with a crystallized vegetable protein.<sup>3</sup> His dosage was gradually increased from 0.2 to 1 cc. His results were more or less similar to those of Holler. Both concluded that this form of treatment was a valuable adjunct to the alimentarium and in many ways was much more reliable than the classic medical treatment of the day. They differed somewhat in their method of administering the drug; Holler placed his patients in bed, while Pribram asserted that one of the most marked advantages lay in the economic side, i.e., the treatment could be given to ambulatory patients in such a manner that they did not lose time from work. At that time, such a condition was important in Germany.

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Address delivered before the American Gastro-Enterological Association, April 30, 1928.

\* From the Gastro-Intestinal Clinic of the Johns Hopkins University School of Medicine.

1 Holler. Ist eine Organische Vaguserkrankung die Ursache des Ulcus Ventriculi Chronicum beim Menschen? Die Grundlage zu einer neuen Therapie des Ulcus Ventriculi und Duodeni, Wien klin Wchnschr **34** 223, 1921.

2 Pribram. Parenteral Reizbehandlung des Magen- und Duodenalgeschwüre, Med Klin **18** 958, 1922, Proteintherapie und chirurgische Therapie des Magengeschwüre, Klin Wchnschr **2** 2112, 1923, Proteintherapie und chirurgische Therapie des Magen- und Duodenalgeschwüre, Deutsche med Wchnschr **51** 141, 1925.

3 The crystallized vegetable protein used was novoprotein.

During the next few years, a considerable number of articles dealing with the problem appeared in Germany. Von Friedrich<sup>4</sup> used various types of protein and came to the conclusion that the crystallized vegetable protein was the best. His results were much less satisfactory than those of Holler and Pribram. Perutz<sup>5</sup> saw good results in post-operative recurrences of ulcers.

Although von Hertlein<sup>6</sup> saw decided benefit, he did not believe that the ultimate results were better than those of the old method. Baake,<sup>7</sup> however, was quite enthusiastic. Kalk<sup>8</sup> had excellent results in about 60 per cent of his cases. In a rather large series—most of which gave indisputable x-ray evidence of ulcer—Grote and Bergman<sup>9</sup> found that 69 per cent of their patients were greatly helped or cured. Hampfel<sup>10</sup> used the method frequently with good results.

All observers agree that the first result of the injection was disappearance of pain, in a great many cases, this is followed by a gradual cessation of other symptoms until frequently all symptoms have disappeared. This has usually happened by the third or fourth injection. Most of the physicians prefer to give the material intravenously, and practically all agree that a slight degree of reaction is necessary, their feeling being that there is direct improvement in proportion to the amount of reaction—recognizing that this must of course, be kept within fairly restricted limits. Holler thought that without a fairly severe reaction results are not to be expected. Pribram was much more conservative and with Baake, Perutz and Kalk, thought that the reaction should be kept at a minimum, this minimum being distinctly necessary. Von Friedrich did not see any relation between the degree of reaction and improvement.

The vaccineurine which was at first used by Holler, Perutz and von Friedrich and which was made from *Staphylococcus aureus* and *Bacillus prodigiosus* was discontinued on account of the severity of the reaction. Practically all of the physicians previously mentioned as well as several others relied entirely on the crystallized vegetable protein.

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4 Von Friedrich. Proteintherapie der peptischen Geschwüre, Arch f Verdauungskr **24** 75, 1925, Zur Frage der Proteinkörpertherapie des Magen- und Duodenal-geschwüre, München med Wchnschr **11** 428, 1925.

5 Perutz. Parenteral Eiweisstherapie beim Ulcus Ventriculi, München med Wchnschr **52** 1527, 1923.

6 Von Hertlein. Ueber die Anwendung des Novoprotins beim Ulcus Ventriculi und Duodeni, Mitt a d Grenzgeb d Med u Chir **35** 15, 1925.

7 Baake. Die Proteinkörpertherapie beim Magen- und Duodenal-ukus. Mitt a d Grenzgeb d Med u Chir **38** 404, 1925.

8 Kalk. Erfahrungen mit Proteinkörpertherapie des Ulcus Duodeni und Ventriculi, Klin Wchnschr **28** 1310, 1923.

9 Grote and Bergman. Ueber Novoprotin Behandlung des Magengeschwüre, Zentralbl f inn Med **45** 337, 1924.

10 Hampfel. Die Proteinkörpertherapie mit Novoprotin speziell beim Ulcus Ventriculi noch Pribram, Med Klin **26** 901, 1923.

given intravenously Latei, Ceranke<sup>11</sup> reported good results with the use of a casein preparation

A comparison of the accumulated reports of many writers reveals the following rather interesting observations (a) In the majority of cases, there is a slight fall in gastric acidity at the end of treatment A repetition of the gastric analyses in these cases at a later date showed that the acidity was within normal limits In a fair proportion of the cases there was no change, and in a few there was a rise in the gastric acidity (b) The roentgen-ray examinations in these same cases show varying results Ceranke reported disappearance of the shadow defect in 25 per cent of his cases, Kalk in 8 per cent and Pribiam in 7 per cent They all agreed that frequently the amount of spasm is markedly diminished or the tonicity becomes normal

Hampfel, von Gromer,<sup>12</sup> Berger,<sup>13</sup> and Pribiam were all particularly enthusiastic in the use of the crystallized vegetable protein in cases in which medical treatment has been tried for a considerable time without avail Pribiam particularly advised using it when pyloric obstruction appeared to be present Under the influence of the protein this obstruction disappeared and would seem, therefore, to have been due to spasm

Pribiam advised giving the crystallized vegetable protein in a course of ten injections, at intervals of from two to four days At the end of this time, if symptoms still persisted, he gave another course In an article appearing in 1925, he came to the conclusion that any patient going through three cases of treatment without improvement should be operated on

The new method has naturally been opposed In making histologic studies on patients coming to operation Marx<sup>14</sup> could not find any signs of healing in those who had been treated To meet the rather sensible objection of the protagonists that this was to be expected since only the patients whose treatment had been unsuccessful came to operation, Gohrbrandt<sup>15</sup> told of some of his operative and histologic experiences He did not believe that any conclusion can be drawn from macroscopic examination of ulcer tissue For various reasons which were not connected with the symptoms of ulcer, he operated on several patients who

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11 Ceranke Ueber den Erfolg der Reizkorpertherapie bei Ulcus Ventriculi und Duodeni, *Wein Arch f inn Med* **13** 391, 1927

12 Von Gromer Die therapeutische Wirkung des Novoprotin bei Ulcus Ventriculi, *Med Klin* **22** 991, 1926

13 Berger Ueber Novoprotin Behandlung des Ulcus Ventriculi und Duodeni, *Munchen med Wchnschr* **27** 924, 1924

14 Marx Zur Wirkung der Proteinkorpertherapie auf das anatomische Bild des Ulcus Ventriculi und Duodeni, *Mitt a d Grenzgeb d Med u Chir* **38** 447, 1925

15 Gohrbrandt Zum anatomischen Bilde der mit Novoprotin behandelten Magen- und Darm-geschwure, *Klin Wchnschr* **4** 2492, 1925

had undergone treatment and were symptom-free In a series of seven patients not only did he find the ulcers still present, but in some of them there was no granulation tissue

#### METHOD OF EXPERIMENT

Twenty-four patients with the history, signs and symptoms and the roentgenographic and laboratory evidence of peptic ulcer were given intramuscular injections of milk proteim These patients were chosen because the evidence from all sides concurred in the diagnosis Other than choosing properly diagnosed cases I have not attempted any other form of selection

Observations extended over a period of eighteen months, but as my interest has increased with time the majority fall within the past six months

Twenty-three men (two of them colored) and one colored woman were treated Their ages were between 24 and 65 Other than peptic ulcer the only complications of interest were psoriasis in one patient, bronchiectasis in one and arthritis in two

A nonspecific milk preparation<sup>16</sup> was used

All patients received the milk preparation deep in the buttocks Care must be taken that one is not making the injection into a deep vein, I have encountered this circumstance twice Injections have been given at irregular intervals The first patients received from one to three injections at weekly intervals, the later ones received from one to seven injections at two to three day intervals The dosage was always at 10 cc

Control roentgenograms were always made, after which the patients were given their first dose of the nonspecific milk preparation Twenty minutes later, they were given a second glass of barium sulphate, and another series of films were taken Films were made at five minute intervals Gastric analyses were done just prior to the control films The Ewald test meal was used, and the stomach content was removed one hour after ingestion

Some of the patients were placed on a soft diet for a week, in a few this was done because they had been on such a diet for months Others were allowed to eat what they wanted

At various times, a second and a third gastric analysis was done, roentgenograms were also repeated

All the patients were ambulatory, most of them being at work while the course of injections was being given

#### OBSERVATIONS

The first change that one notices during the treatment is a marked decrease in pain This may happen after the first injection, and it is infrequent that the pain does not decrease by the second or third This is in itself, of course, rather pleasing to the patient Later on, there is considerable decrease in the other symptoms that accompany the disease Regurgitation, eructation and gaseous disturbances of the abdomen all disappear in proportion to the general degree of improvement obtained by each individual patient This may vary considerably

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<sup>16</sup> The nonspecific milk preparation used was Aolan It is distributed in this country by the H A Metz Laboratories, Inc, New York, which has been kind enough to keep me supplied to the extent of my needs

It is not unusual to have the patient state that on the night following the injection he has some increase of pain, particularly pain caused by gas. As the number of injections increases, less and less focal reaction is observed.

Locally, I have seen a reaction in one patient. This appeared following the third injection and was evidenced by fever, local inflammation and tenderness. The fourth injection five days later produced a much smaller reaction. Following his third dose, one patient had a reaction with nausea, vomiting and chill followed by sweating. In another patient this followed the fourth injection.

The results of the treatment on the gastric secretion in twenty-one patients are shown in table 1. The immediate and late effects were decidedly different. In the first group there was an increase of gastric acidity in five of the seventeen cases, an approximate constancy in nine, and a true decrease in three.

Of these twenty-one cases, eight were observed after a period of from four to eighteen months. In this group there was an increase of acid in two, an approximate constancy in two and a true decrease in four.

The roentgen-ray observations are equally interesting. In fourteen instances films were made from twenty to thirty minutes after the injection of a nonspecific milk preparation. It was not possible in any case to be sure that there was definite relaxation of the muscular tone of the stomach within thirty minutes after the primary injection. This came rather as a surprise, for in light of the excellent work of Muller and Petersen<sup>17</sup> on the effect of injections of foreign protein I was hopeful of obtaining visible evidence of this occurrence. They showed kymographic tracings of contraction of the stomach before and after the injection of the nonspecific milk preparation. The tracings were obtained by inflating a small balloon which the patient had swallowed. This was distended by air and attached to a manometer which recorded the contractions of the muscles of the stomach on a drum. This may be seen in figure 1.

In eighteen instances, films were taken just after the completion of treatment. In one case only was there a disappearance of the shadow defect (figs 2 and 3). In three cases there appeared to be either greater definiteness of the defect or more spasm. In six cases either a smaller defect or markedly less spasm or both were present (figs 4, 5, 6 and 7). In the nine remaining cases, a definite change could not be determined in the x-ray films made at the end of treatment.

As many as eight patients were reexamined from four to eight months after treatment. When this paper was written, five of them showed a smaller defect or less spasm or both. The other three did not show any change.

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17 Muller and Petersen. Ueber die Wirkung der Proteinkorperinjection auf den Magen-innervation, *Munchen med Wchnschr* 74 531 and 588, 1927.

TABLE 1—Summary of Treatment, Laboratory Investigations and Results on Twenty-Four Patients Following Parenteral Injection of Nonspecific Milk Preparation

Case	No. of Interval			Changes in Gastric Acidity			Time Since Last Treatment	Condition of Patient	Changes in Roentgenograms				From 2 to 18 Months Treatment
	Injections	in Days	Interval	Control	End of Treatment	From 4 to 18 Months Later			Control	½ Hour after Injection	End of Treatment		
1	6	7	7	20-36		75-109	Operation	At operation, two healed ulcers, many adhesions	Irritable stomach, defect due to adhesions?		No change	No change	No change
2	6	7	7	26-72	30-70		1 month	Clinically well	Irritable stomach, filling defect in duodenum		Normal stomach and duodenum		
3	12	3-7		60-76	50-70		2 months	Clinically well	Atonic dilated stomach, large duodenal defect, partial obstruction	No change	Good tone, cap almost smooth		
4	10	3-5		0-14	34-60		2 months	Improved	Gastric ulcer niche and hourglass contraction	No change	Less spasm opposite ulcer niche which is smaller		
5	7	3		38-92	32-42	40-62	Operation	At operation, duodenal ulcer	Irritable stomach, defect in pylorus due to spasm?		No change		
6	6	3-6		32-62	48-66		2 months	Clinically well	Irritable spastic stomach, defect in duodenum	No change	More spasm and greater defect		Less spasm and defect
7	12	2-4		62-94	74-88		3 months	Clinically well	Large spastic stomach, large defects in duodenum and pylorus	No change	No change		No change
8	5	3-1		10-52			1 month	Clinically well	Irritable stomach, filling defect in cap due to ulcer				
9	13	3-7		40-72	42-62		Weekly in jections	Improved	Irregularity at duodenum due to operative procedure	No change	Less spasm of stomach		
10	3	5-6		64-96		56-80	15 months	Clinically well	Irritable stomach, filling defect in pylorus	No change	No change		Normal tone, defect same
11	9	5-9		52-68	60-100	72-92	3 months, treatment at intervals	Worse	Large ulceration of pylorus and duodenum	No change	Greater spasm, defect same		

12	8	2-3	60-84	80-110	1 month	Clinically well	Hyperactive filling defect in duodenum	stomach, No change	No change	
13	7	3-4	58-72	60-90	2 months	Clinically well	Hyperactive filling defect in duodenum	stomach, No change	No change	
14	2	7	72-94		18 months	Clinically well	Hyperactive filling defect in duodenum	stomach, No change	No change	
15	2	7	71-92	38-98	6 months	Clinically well	Very irritable stomach, defect in duodenum	No change	More spasm of stomach, defect more pronounced	
16	6	1	10-56	30-46	3 months	At operation, duodenal ulcer	Irritable dilated stomach, large defect in duodenum	No change	No change	
17	6	3-4	40-75	60-88	Operation	Clinically well	Irritable dilated stomach, large defect in duodenum	No change	No change	
18	3	5-6	90-112	20-52	12 months	Clinically well	Large atonic stomach, large defect in pylorus and duodenum, partial obstruction	No change	No change	Normal tone, filling defect same
19	3	7			11 months	Clinically well	Irritable stomach, defect in duodenum	No change	No change	No change
20	7	3-6	58-76	30-70	2 months	Clinically well	Defect in pylorus, markedly irritable stomach	No change	No change	Outline of duodenum seen no change in atonicity
21	3	5-6	50-70		14 months	Clinically well	Large filling defect in stomach, very irritable	No change	No change	
22	4	3-5	42-62	42-64	2 months	Clinically well	Large filling defect in duodenum	No change	No change	
23	1	1-5	30-48	46-64	2 months	Clinically well	Large filling defect in duodenum	No change	No change	
24	5	3-4	84-98	34-52	2 months	Clinically well	Atonic stomach, filling defect in duodenum, partial obstruction	No change	No change	
					2 months	Clinically well	Irritable spastic stomach, filling defect in duodenum	Normal stomach, filling defect in duodenum	Less spasm and defect	
					2 months	Improved	Very spastic stomach, duodenal ulcer	Normal tone defect same		



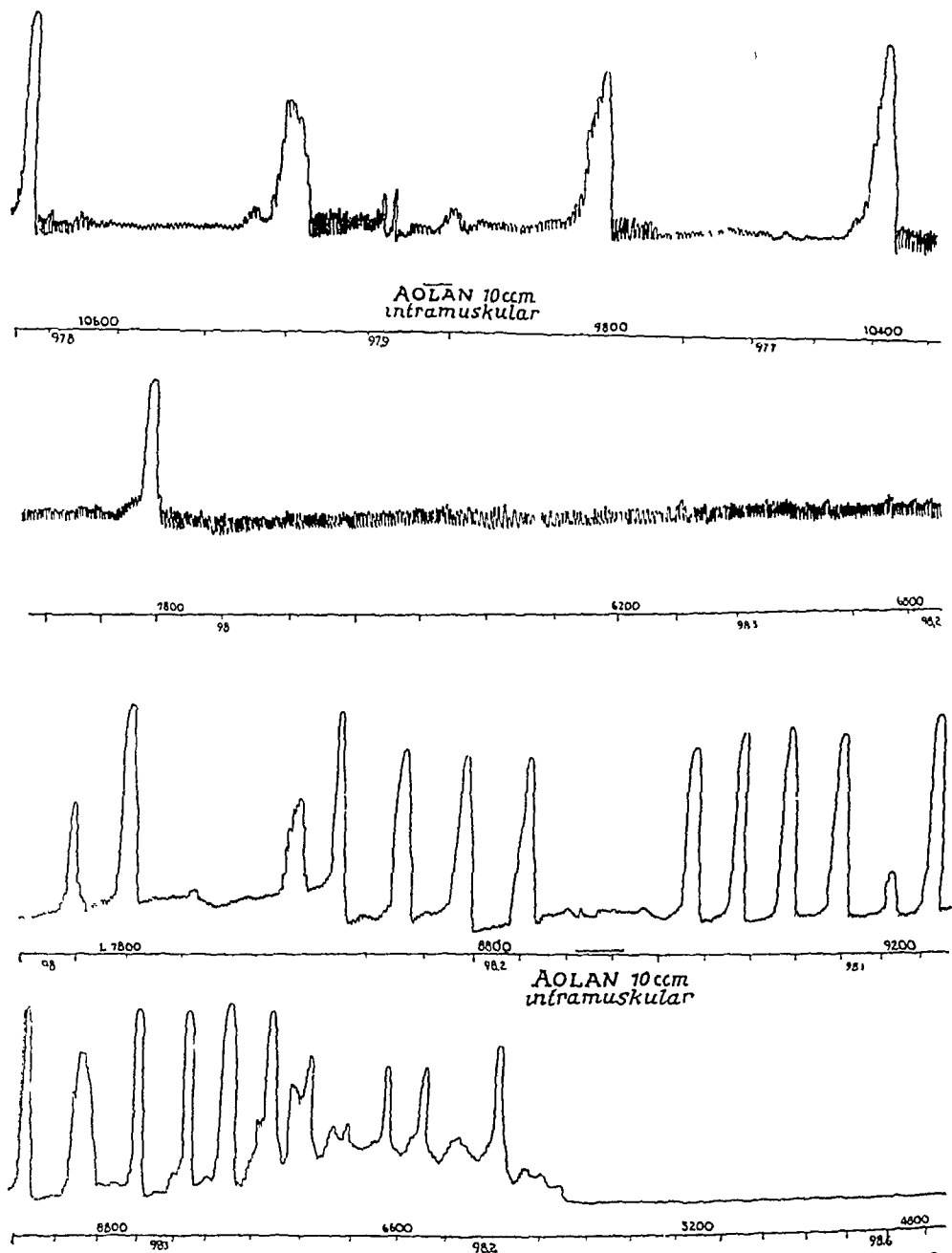


Fig 1—Inhibitory effect of intramuscular injection of 10 cc of a nonspecific milk preparation on gastric contraction in two patients Taken from Muller and Petersen

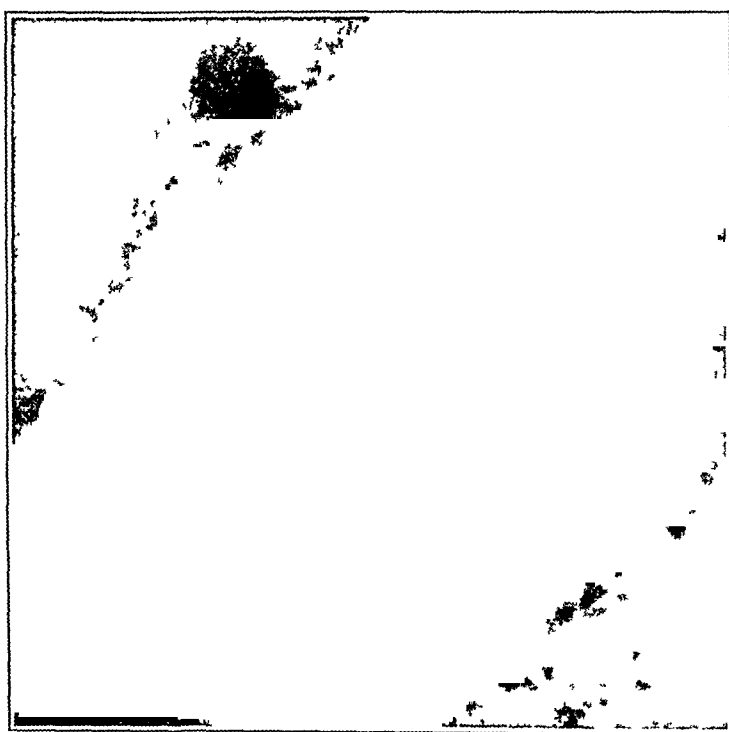
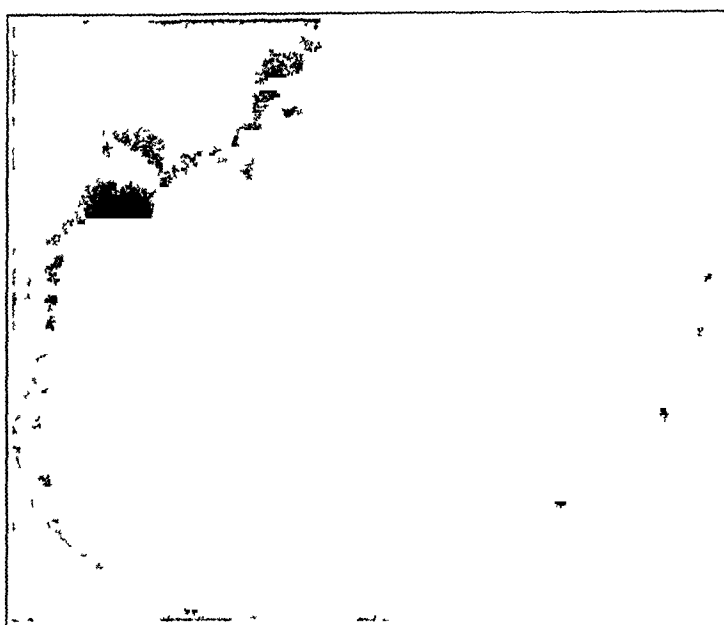


Fig 2 (case 2) —Duodenal ulcer in control

Examinations of the stools for the presence of occult blood were made on all except two patients. The benzidine slide method was used. Twelve were found to give positive tests. This did not persist long in any instance.

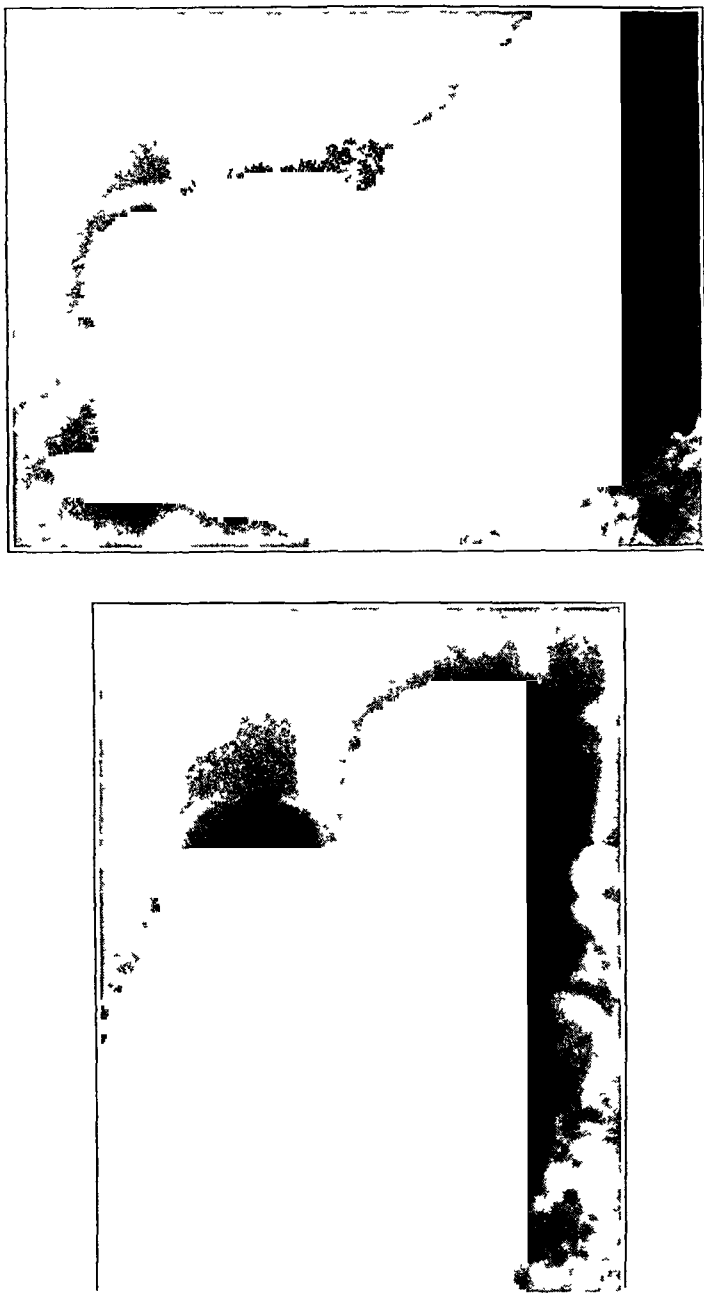


Fig 3 (case 2) —Normal stomach and duodenum at end of treatment

It is not a rare occurrence to have patients complain of constipation while they are taking the course of treatment. A control film and one taken during treatment in case 17 may demonstrate the cause (figs 8 to 10)

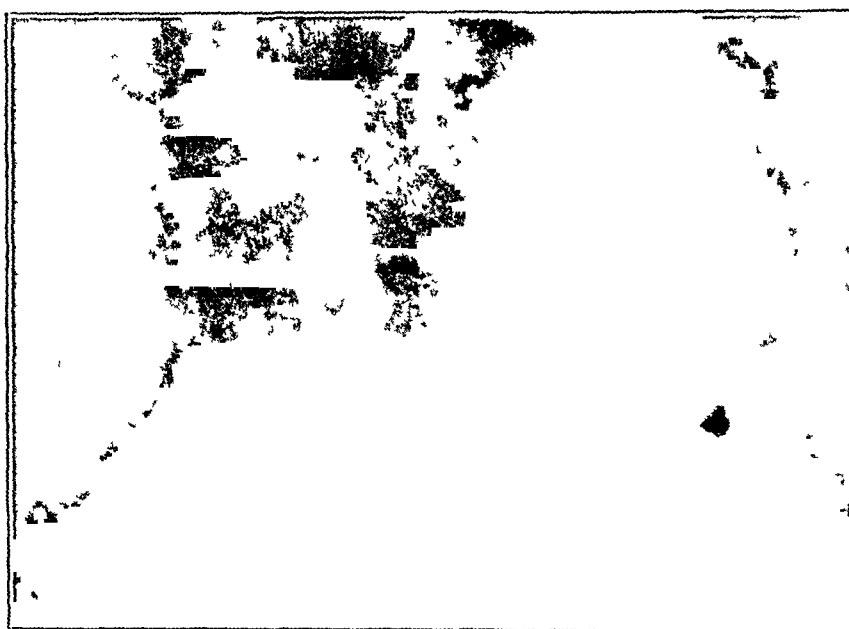
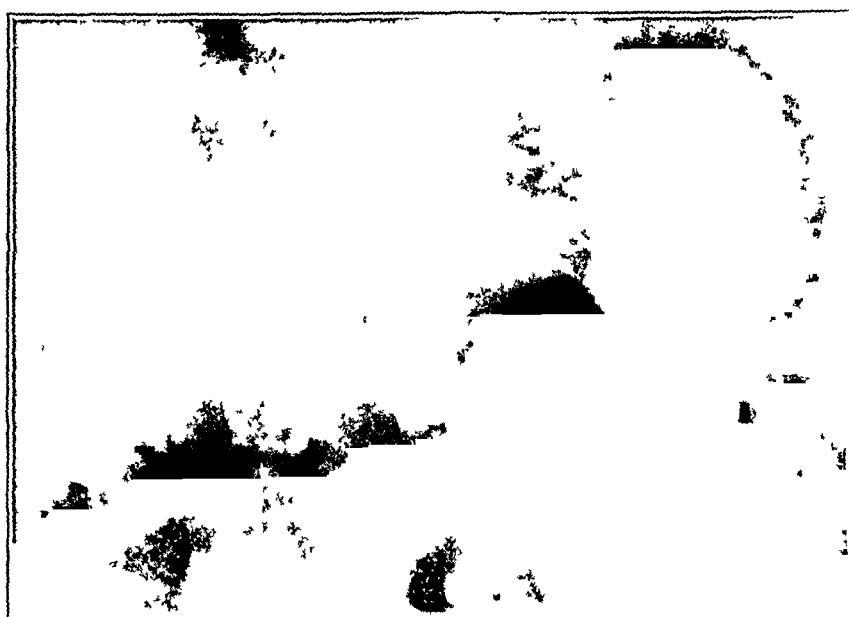


Fig 4 (case 14) —Tremendous irritability and spasm and duodenal ulcer in control

Before I consider the clinical results in these twenty-four patients, it may be wise to divide them into two classes, namely those with acute and those with chronic cases. In the first class are included all those patients who were having their first attack or their second or third after a period of well-being lasting more than from four to six months. In the second class are placed those who have had symptoms at varying intervals for years, those who are fairly comfortable while receiving

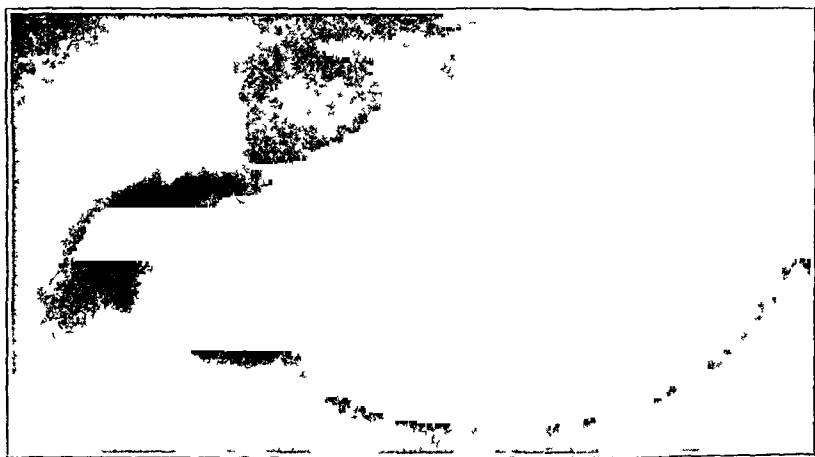
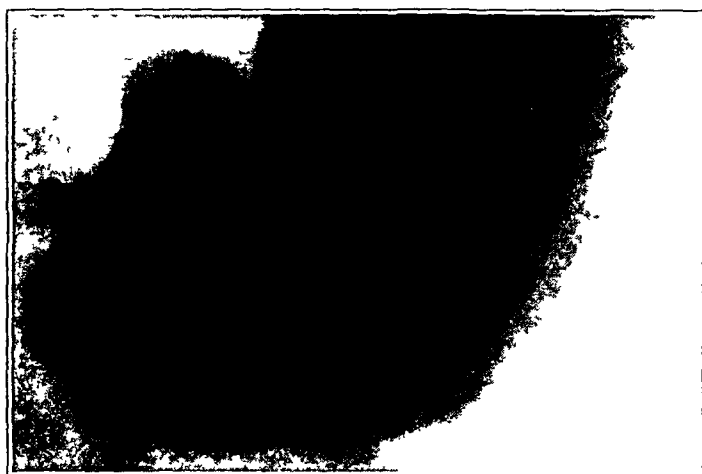


Fig 5 (case 14) —Eighteen months after treatment, showing good tone and duodenal defect

treatment but who have a relapse when treatment is stopped and those who have had many acute attacks and are now suffering constant discomfort. Fifteen patients were considered to be suffering from acute ulcers and nine from chronic ulcers. Twelve of the former are entirely without symptoms, two are decidedly better and one is worse. Among the nine patients with chronic ulcers, five are without symptoms, although two of them had partial pyloric obstructions, one is much better and three were operated on for relief from symptoms.

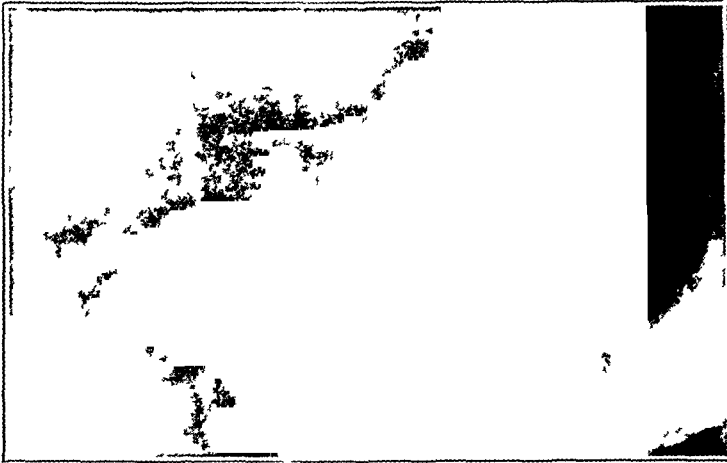


Fig 6 (case 10) —Spastic stomach and duodenal defect in control.

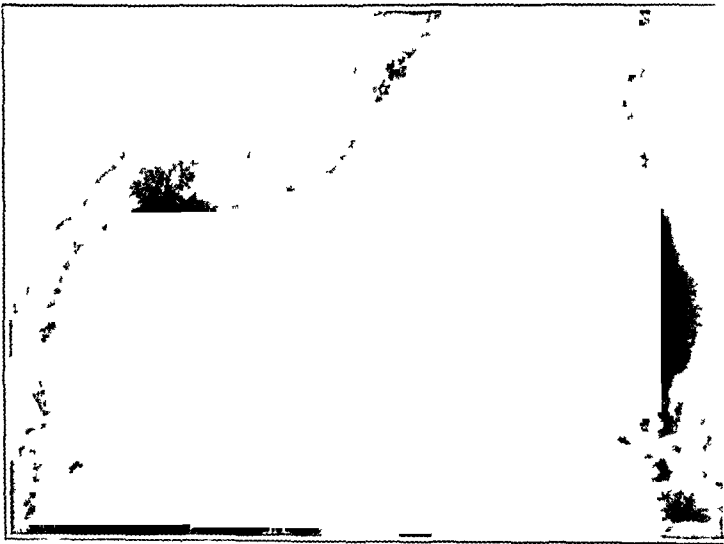


Fig 7 (case 10) —Sixteen months after treatment, showing smaller defect and perhaps less spasm

If this is placed on a percentage basis 80 per cent of the patients with acute forms of the disease are symptom-free. If one includes with them the same type of chronic case, one finds that 66.6 per cent of all patients have been clinically cured. The percentage of cure or betterment in both groups is 83.2. It is also necessary to bear in mind that after the first week almost all these patients ate all manner of food.

Only three patients came to operation, two of them showed ulcers on the anterior surface that were not remarkable. The third case showed marked adhesions about the duodenum and gallbladder without constriction of the pylorus, there were two healed ulcers in the duodenum. Gastro-enterostomies were done on all these patients, so sections could not be made (table 2).

## COMMENT

There is no doubt that one may obtain remarkable results in the treatment of these patients by the intramuscular injection of milk pro-

TABLE 2—*Clinical Results on Twenty-Four Patients*

	Well	Improved	Per Cent Combined	Worse	Operated On	
					Number	Per Cent
Acute	12	2	93.3	1	0	0.0
Chronic	5	1	66.6	0	3	33.3
Total	17	3	83.2	1	3	16.8

tein. This fact in itself, although interesting, is not of great therapeutic value unless the improvement so obtained is stable. As already noted, twelve of the fifteen patients with acute forms are entirely without symptoms and have been so for from two to fifteen months. Only five of them have been under observation for more than a year, they are all clinically well. The remainder have been symptom-free for from three to ten months. It is also important to note that these patients have been on a full diet. Two patients with acute forms of the disease have been improved and have preferred to remain in this state rather than be operated on. One has become decidedly worse after a temporary improvement and will, in my judgment, come to operation.

Among the chronic cases there have been some startling results. One patient has been well for eighteen months. He received only two injections of the nonspecific milk preparation, and as he was the first patient treated the injections were given a week apart. In spite of this remarkable result, if he came to me today for the first time he would receive from five to seven injections at intervals of from two to three days. The latter method of timing gives good results, but it too may be changed later. The patient in case 15, whose recovery was the most remarkable of all, had been sick for twenty years. For six months, he had been

in constant pain and discomfort. Four days after the initial injection, he was practically without pain. He received one more injection and was allowed to go home. He reported after a period of six months that he had been entirely well except for an occasional mild attack of gas disturbance. The other three patients who are now clinically well had all suffered for years. One of them had had a gastro-enterostomy done

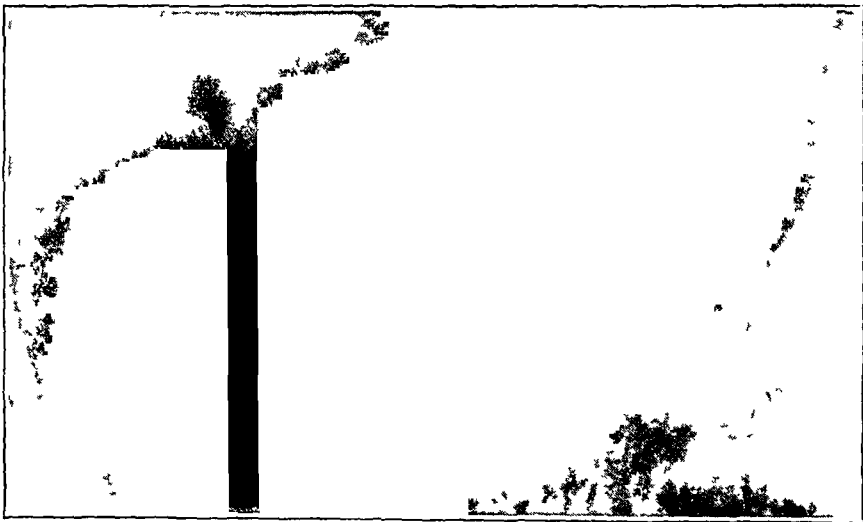


Fig 8 (case 17) —Duodenal ulcer with marked six hour retention in control

five years before I saw him, since then he had had many recurrences and had been miserable for six months, just prior to treatment with the nonspecific milk preparation. His pain disappeared after three injections, and for the next three weeks he was without symptoms. They suddenly reappeared in great intensity, but were controlled by a second series of injections. At the time this paper was written, he had been well for two months.



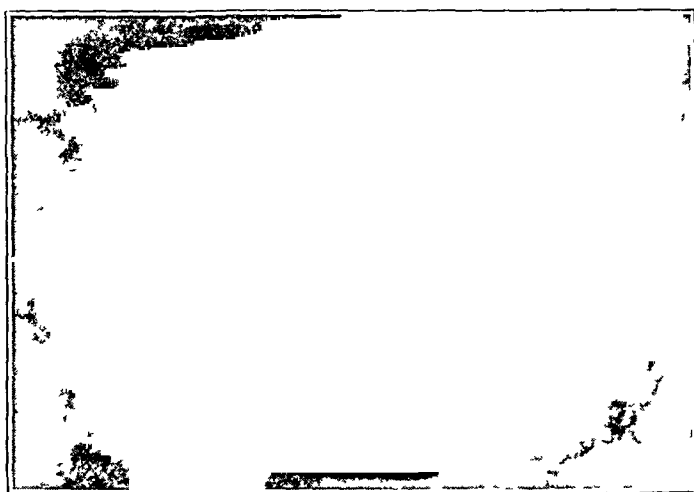
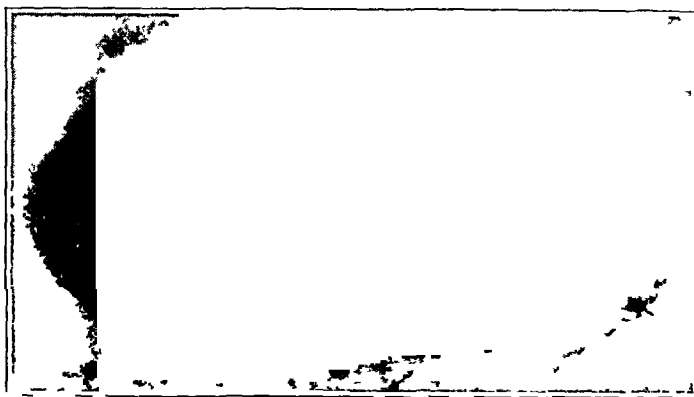


Fig 9 (case 17) —Appearance during treatment Complaint, constipation  
Spastic small intestine

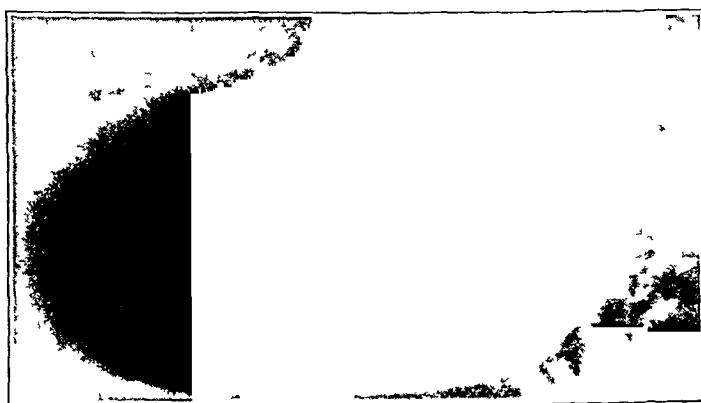


Fig 10 (case 17) —End of treatment Hazy outline of cap

Case 1 offers an interesting study. The patient had had many recurrences in the past four or five years. In spite of medical treatment his condition had been getting gradually worse for the past year or so, and during the month before the first injection was made his condition was one of great discomfort. He received three injections before his pain left, and he remained markedly improved for six months although he had moderate discomfort from gas. One month before admission his pain returned, and it could not be controlled by the nonspecific milk preparation. At operation, two healed ulcers and many adhesions were found. There was no obstruction.

Cases 16 and 5 are still a mystery to me, for it would seem that the same good results should have been obtained in them as in the others. The former did not show the slightest improvement. At operation, a

TABLE 3—*Individual Chart*

Case 15									
Date	Nonspecific Milk Preparation	Vomiting	Stool	Gastric Analysis	X Ray	Diet	Pain	Intensity of Symptoms	Course of Symptoms
Jan 18	+	0	0	74 & 92	Ulcer of pyloric duodenal region	Regular	+++	+++	—
Jan 20	—	0	—	—	—	—	+	+	Feels better
Jan 25	+	0	0	—	—	—	0	0	No symptoms
March 1	—	0	—	—	—	—	0	0	No symptoms
April 23	—	0	0	60 & 70	No change	—	0	0	No symptoms, has gained 10 pounds (4.5 Kg.)
June 13	—	0	—	30 & 46	No change	—	0	0	No symptoms, has gained 4 pounds (1.8 Kg.) more

fairly large ulcer was found. There was no obstruction. The patient in case 5 did exceptionally well after one injection. He had been on good medical treatment for months, and the pain which had been present for three months and which could be relieved only by codeine sulphate disappeared in twelve hours after one injection. He was so completely without symptoms that he did not receive any more of the nonspecific milk preparation. Four months later symptoms returned with all their former intensity. Six injections did not give any relief. At operation, a typical duodenal ulcer was found.

The patient in case 9 had a ruptured duodenal ulcer five years before I saw him. The leak was repaired with a purse-string suture. He had several recurrences and in the last three months did not obtain relief from good medical treatment. After some experimenting it was found that he could be kept practically symptom-free if he received one injection each week or ten days.

Tables 3, 4 and 5 better demonstrate the typical changes observed in some of the patients.

## DOSAGE

The question of dosage is far from being settled. As already noted, 10 cc. of a nonspecific milk preparation has been the amount used for each injection. In case 8 a local reaction similar to the Arthus phe-

TABLE 4—*Individual Chart*

Case 16									
Date	Nonspecific Milk Preparation	Vomiting	Stool	Gastric Analysis	X Ray	Diet	Pain	Intensity of Symptoms	Course of Symptoms
April 2	+	0	0	46 & 56	Ulcer of duodenum	Soft	++	++	—
April 9	+	0	0	—	—	—	+	++	No change
April 16	+	0	—	—	—	—	0	±	Feels much better
April 20	+	0	—	—	—	—	+	+	Complains of much gas
April 24	+	0	—	60 & 88	No change	—	+	+	No improvement
May 1	+	0	—	—	—	—	+	+	No improvement
May 9	—	0	—	—	—	—	+	+	Operation, posterior gastro-enterostomy for the ulcer
June 4	—	0	—	—	—	Regular	0	0	No gastrointestinal symptoms except some gas

TABLE 5—*Individual Chart*

Case 17									
Date	Nonspecific Milk Preparation	Vomiting	Stool	Gastric Analysis	X Ray	Diet	Pain	Intensity of Symptoms	Course of Symptoms
April 2	—	+	++ blood	40 & 75	Ulcer at pylorus, atonic stomach	Soft	++	++	—
April 4	+	+	++ blood	—	—	Soft	++	+	—
April 9	+	0	+ blood	—	—	Soft	Very little	±	Feels much better
April 13	+	0	0	—	—	Regular	0	0	Feels almost well
April 16	+	0	0	—	—	—	Slight pain ½ hour once	±	—
April 19	+	0	0	—	—	—	0	0	Feels like another man
April 27	—	0	0	10 & 30	No change	—	0	0	No symptoms
June 1	—	0	0	—	—	—	Very slight at times	±	Working hard
June 15	—	0	0	20 & 30	Smaller stomach	—	0	0	No symptoms
July 1	—	0	0	—	—	—	—	0	No symptoms

nomenon was produced. The general reactions were probably due more to the presence of a foreign body than to the fact that the patient had been sensitized. In one case the reaction followed the last of these weekly injections (case 18) and in the other, the fourth injection (case 20). The reactions were not nearly so severe as those usually seen after transfusions.

A comparison of the results obtained in relation to the time intervals between injections reveals satisfactory results following any sequence, but work now under way makes me think that shorter and more regular intervals will produce the best and most lasting results

#### CONCLUSION

In three cases not included in this series, in which previous gastro-enterostomies or resections had been performed and in which the symptoms of the patients presented a picture much more typical of adhesions than recurrent ulcerations, help was not obtained with a nonspecific milk preparation

If the cases are followed entirely from the point of view of improvement in laboratory studies, it is true that few changes can be demonstrated. However, when one sees the disappearance of that pinched, haggard look, the resumption of an upright carriage, an ability to eat heartily without fear of consequences and the usual gain in weight and when one realizes that numbers of these men had had previous treatments without avail, one cannot help but be impressed with the results of this form of treatment

Many excellent results are obtained by the classic medical treatment for ulcer, and time alone will show whether the parenteral injection of a foreign protein offers a more permanent cure. Whatever the future may demonstrate, certainly, the effect of the nonspecific milk preparation on pain and its results when other methods have failed will justify its retention in the therapeutic armamentarium

#### REPORT OF CASES UP TO JULY 12, 1928

CASE 1—A white man, aged 48, complained of almost constant pain in the upper part of the abdomen which had been present for about six months, was not relieved by ingestion of food and was increasing in its intensity. His first attack, which occurred five years before admission to the hospital, consisted of a gnawing hunger pain which came on two or three hours after meals and which was relieved by food. Up to six months before admission he had many of these attacks, which lasted from four to seven weeks each, and between attacks he did not have any complaints

Physical examination showed a tired man who had lost weight and looked bad. There was considerable tenderness in the midepigastria area. The gastric analysis was free acid, 20, and total, 36. Occult blood was not present in the stools. The x-ray films showed a stomach which was tremendously irritable and which had a filling defect in the duodenum. On Nov. 11, 17 and 27, 1927, he was given 10 cc of a nonspecific milk preparation. There was complete relief from pain, but he still complained of gaseous distention and fullness. These symptoms continued until May, 1928. The gastric acidity was free, 75, and total, 109, x-ray examination did not show any change except less gastric spasm. At this time pain recurred which was not alleviated by three injections of a nonspecific milk preparation. At operation, two healed ulcers and many adhesions were found. Following a gastro-enterostomy, he obtained complete relief. He was always on a regular diet.

CASE 2—A white man aged 32 complained of epigastric pain for the first time. For two weeks he had had a gnawing pain in the upper part of the abdomen which was relieved by food and which appeared two or three hours after meals. His appetite was good and he had not lost weight. On physical examination, nothing of note was determined. The stool gave a faintly positive test for occult blood, and the gastric analysis was 26 and 72. On the x-ray films a filling defect was seen in the duodenum, and the stomach was irritable. He was given 10 cc of a nonspecific milk preparation on May 1, 7, 15 and 23 and on June 6 and 13. He was kept on a regular diet and all symptoms disappeared after the second injection. At the end of treatment, the gastric analysis was 30 and 70, the x-ray films were entirely normal. At the time this paper was written, he was clinically well.

CASE 3—A white man, aged 65 had complained of pain in the upper part of the abdomen for the past five months. It had been acute and accompanied with nausea and vomiting for the past three weeks. For fifteen years he had been having recurrences of a gnawing hunger pain in the epigastrium which at first had been relieved by food or soda. During the interval between the attacks, his general health was excellent. In more recent years, each attack left him feeling a bit weaker and more easily upset. The attack which brought him to the clinic was by far the worst, and nausea, vomiting and anorexia occurred for the first time.

On physical examination, the patient appeared tired, worn, bent and old with a haggard, pinched expression. The blood pressure was 100 systolic, 60, diastolic and he had an occasional extrasystole. He was markedly below weight and complained bitterly of pain when light pressure was made over the epigastrium. The gastric analysis was 60 and 76, examination of the stool showed occult blood. In the x-ray films an atonic stomach with a large filling defect in the duodenum was seen. He was given 10 cc of a nonspecific milk preparation on April 24, 27 and 30, May 2, 3, 11, 14 and 23 and on June 7, 11, 15 and 18. After four injections, he was symptomless. Occult blood was not found in the stools, and he was put on a regular diet. On May 27 the gastric acidity was 50 and 70, and in one x-ray film the entire duodenum was visualized, the tone of the stomach showed great improvement.

On June 7 the symptoms returned but in a much less severe form. After four injections of the nonspecific milk preparation, he was again in excellent condition and remained so until the time this paper was written. He looked like a different person, walked with an upright carriage and was back again at his work.

CASE 4—A man aged 44, complained of a severe gnawing pain in the pit of his stomach. For six years he had had recurrent attacks of gnawing hunger pain in the epigastrium which at first was relieved by food, but in the attack that had persisted for six months prior to admission food had less and less ability to help, and the pain was present almost constantly. A great deal of gas was present, but in spite of all this his appetite was good, and he had not lost weight.

Physical examination showed nothing of importance except marked spasm and tenderness in the upper part of the abdomen, especially in the midepigastrium. The stool did not show blood, and the gastric analysis did not reveal any free acid but a total acidity of 14. Fluoroscopic examination showed a niche on the lesser curvature and a marked irregularity at the pylorus. On the x-ray films repeated examinations had not shown the niche, as it was presumably a bit on the posterior surface, the films did, however show the pyloric irregularity. On May 4, 9, 12, 15, 19, 22, 29 and on June 5 and 19, 1928, he was given 10 cc

of a nonspecific milk preparation, and although his symptoms were not completely cured he was so much better that he would not consider operation. The last gastric analysis was 34 and 60. The fluoroscopic examination of the stomach showed a smaller niche. He was on a soft diet for months.

CASE 5—A masseur, aged 28, had been having gastric symptoms for about two years. The previous attacks had lasted for from four to six weeks and had been relieved by routine medical treatment. On admission, he complained of epigastric pain which had been present for six months and for which codeine sulphate had been given recently as the only alternative to constant pain. Except for considerable tenderness and spasm in the epigastrium, the physical examination gave negative results. Gastric analysis was 68 and 92, and the stool contained occult blood. X-ray films showed an irritable stomach with a lateral cap, but a definite ulcer was not made out. On Feb 8, 1928, he was given 10 cc of a nonspecific milk preparation. Twelve hours subsequently his pain entirely disappeared, and he was without symptoms for four months. During the period of well-being, the stools were normal, the gastric acidity was 32 and 42, and the x-ray films unchanged. On May 12, the symptoms recurred with all their initial intensity. Five injections of the milk preparation were of no help, and he was operated on, May 25. A large, inflamed, indurated ulcer was found, and, owing to the presence of many adhesions from a previous peritonitis, it was necessary to do an anterior gastro-enterostomy. Relief was immediate and absolute.

CASE 6—A white man, aged 28, complained of an attack typical of many he had had in the past four years which lasted from four to eight weeks with periods of complete relief in the interim. The symptoms were gnawing hunger pains which food relieved for two or three hours and which awakened him at night. There was considerable gaseous distention and acid eructation. His appetite was good, and he had not lost weight. The symptoms which brought him to the dispensary had been present for about two or three weeks and were not showing any signs of abatement.

Physical examination showed nothing of importance except ragged tonsils and a tender area in the midepigastrium. The stool gave a positive test for blood, and the gastric acidity was 32 and 60. The x-ray films showed a filling defect in the duodenum and an irritable stomach. A nonspecific milk preparation in 10 cc amounts was given April 23, 27, 30 and May 2, 10 and 16, 1928. There was complete relief from symptoms after the fifth injection, and he had remained free from symptoms up to the time this paper was written. At the end of treatment the gastric analysis was 48 and 66, the stools did not contain blood, and the filling defect in the x-ray films was smaller, gastric spasm had also decreased. He was on a regular diet and, furthermore, on June 15 developed acute gonorrheal urethritis without gastric symptoms.

CASE 7—This case was extremely interesting and quite instructive. Five years before admission, the patient developed symptoms of duodenal ulcer and, not being helped by medical treatment, was operated on and a duodenal ulcer found. A pyloroplasty gave him relief for a year, but in the past three years he had severe attacks similar to those prior to operation, and blood had been found in the stool. Twice he had been subjected to the so-called Sippy cure. Between attacks he felt well. On admission, he complained of an epigastric pain of five weeks' duration which was not helped by food. He was 44 years old.

On physical examination the man looked cadaverous and was bent over with pain, which he localized in the epigastrium. There was tenderness at this point, and marked muscle spasm was present. The hemoglobin was 74 per cent (Sahli), and the stools contained occult blood. Gastric analysis showed free acid, 62 and

total acid, 94, and on the x-ray films marked irritability of the stomach was seen. He responded slowly to a nonspecific milk preparation which was given in 10 cc amounts on April 13, 15, 19, 23 and 27, on May 2, 15, 16, 19, 22 and 28 and on June 4, but after the third injection he felt a great deal better and began to walk with an upright carriage. At the completion of the sixth treatment he felt quite well and continued so until May 15, when another course of the milk preparation was necessitated by a return of symptoms. After that, he remained well. Blood reappeared in the stools on the recurrence of symptoms but was not found on discharge. After the second series of injections the free acid was 74 and total acid 88, and the x-ray films were unchanged. He gained 10 pounds (4.5 Kg), ate a regular diet and felt extremely well. He looked like a different man.

CASE 8—L. W., the only woman in the series, an intelligent negro cook, for five years had had autumnal recurrences of epigastric gnawing pain which were temporarily relieved by food and which usually lasted from four to eight weeks. For several years, she had had a moderate degree of arthritis. On admission she had been having gastric symptoms for six weeks, this was the first attack to occur in the spring.

The physical examination showed a mild arthritis of the knees and some tenderness in the midepigastrium. Gastric analysis was 40 and 52, and the x-ray films showed an irritable stomach and a deformed cap. Blood was not found in the stool. A nonspecific milk preparation in 10 cc amounts was given on May 9, 12, 15 and 17, 1928. Following the third injection, the patient developed a large local reaction (Arthus' phenomenon), due to a misunderstanding, she received a fourth injection, but fortunately the reaction was much less intense. The gastric symptoms practically cleared up, and the arthritis was entirely relieved.

CASE 9—A man, aged 46, had his first symptoms three years before admission in perforation of a duodenal ulcer, at operation, a simple purse-string suture was made for a closure. He came to the clinic complaining of pain of three weeks' duration in the epigastrium, more intense one or two hours after eating and temporarily relieved by food. Previous to this he had had three similar attacks, he had been admitted to the hospital and had received the Sippy treatment.

On physical examination, the man was underweight and tired and was bent over from pain and an epigastrium which was tender on palpation. The stool contained occult blood, and the gastric analysis was 40 and 72. Without knowledge of the history, Dr. Baetjer interpreted the x-ray films as follows: "Defect in duodenum due to operative interference." The patient was put on a soft diet and given a nonspecific milk preparation, 10 cc at a time, on March 26 and 28, on April 9, 16, 19 and 25, May 2, 7, 15 and 21 and on June 1. There was some immediate improvement in the first three weeks, and in the next six he was kept fairly comfortable on one injection a week. During the following six weeks he was without symptoms. At the time this paper was written, he was on a soft diet and had gained 8 pounds (3.6 Kg).

CASE 10—A man, aged 28, came to the clinic complaining of gnawing hunger pains in the epigastrium which came on when the stomach was empty and which were relieved for two or three hours by food. The attack had been active for four weeks and was similar to four previous ones which had occurred during the last three years. His appetite was good, and he had not lost weight although he was a steel roller.

Physical examination gave essentially negative results. The stool contained blood, and the gastric analysis showed free acid, 64 and total, 96. On the x-ray

films a filling defect was found at the pylorus and the stomach was irritable. The patient was given 10 cc of a nonspecific milk preparation on March 31 and on April 4 and 7, 1927. Symptoms and occult blood disappeared after the second injection and did not return. Later, the gastric analysis was 56 and 80. On the x-ray films the stomach was normal in tone, but the pyloric defect was still present.

CASE 11—A very sick man, aged 46, presented himself at the clinic complaining of constant pain in the stomach, of inability to eat and of a steady increase in intensity of symptoms of three weeks' duration. Four years before admission, he had had an attack of gnawing pain in the epigastrium which lasted about six weeks but which was temporarily relieved by food and soda. At that time his appetite was good, and he had not lost weight.

On physical examination the man was found to be sick, worn out, in considerable pain and markedly underweight. There was marked spasm of the upper rectus muscles and tenderness on light palpation. The gastric analysis was 52 and 68. The stools contained occult blood. On the x-ray films there was a large defect in the pylorus with a probable perforating ulcer. The patient would not consent to operation, consequently, he was placed on a soft diet and given a nonspecific milk preparation in 10 cc amounts on April 16, 18, 21, 24, 27 and 30. Pain and bleeding disappeared after the second injection, and the gaseous distention was practically relieved by the end of the treatment. He gained weight and looked well. The gastric analysis was not done, but the x-ray films were unchanged.

Five weeks after the end of treatment the symptoms returned, as did the previous local abdominal pain. The gastric analysis was 72 and 92, and the x-ray films were unchanged. The milk preparation was again given on June 5, 11, 13 and 19 without relief. On June 24 he had a hematemesis and will, I believe, now consent to be operated on.

CASE 12—A man, aged 47, entered the dispensary complaining of symptoms of two weeks' duration exactly similar in kind but greater in degree than those which brought him to the dispensary one year before when the condition was diagnosed as duodenal ulcer and the patient placed on routine medical treatment and evidently cured. On the return of the gnawing hunger pain, which was temporarily relieved by food, he had reinstated the same procedure but without help. He had lost his appetite and was very uncomfortable.

On physical examination, the man had a pinched face, was somewhat below weight and was quite tender in the midepigastrium. Blood was not found in the stools, the gastric analysis was free acid, 60, total, 84, and the x-ray films showed a large filling defect in the duodenum and an irritable stomach. On May 2, 4, 7, 9, 11, 15 and 18, he was given a nonspecific milk preparation in 10 cc amounts. The symptoms entirely disappeared after the third injection. He began to gain weight and by the end of the treatment had put on 8 pounds (3.6 Kg). The x-ray films at this time were unchanged. The gastric analysis was 80 and 110. The condition is cured clinically.

CASE 13—A negro, aged 37, complained of a gnawing pain in the pit of his stomach, his appetite was good, but he was afraid to eat. The pain awakened him at night, and the attack had been active for ten days. In the previous two years, he had had four or five similar attacks.

The physical examination gave negative results. There was no blood in the stool. The gastric analysis was 58 and 72. The x-ray films showed a filling defect in the duodenum. He was given 10 cc of a nonspecific milk preparation on May 21, 23 and 28 and on June 4, 7, 11 and 18, 1928. After the second



injection, the symptoms had vanished. At the end of treatment, the gastric analysis was 60 and 90. The defect in the duodenum seemed more pronounced and the stomach more spastic in the x-ray films. He was always on a regular diet and was considered cured clinically.

CASE 14—A man, aged 32, complained of a severe gnawing pain which started in the midepigastrum and at times spread over the entire abdomen. Neither food nor soda gave relief. His appetite was poor, and the pain kept him awake at night. In the two years before admission he had attacks in the fall and spring which lasted four or six weeks, but at these times food or soda gave relief and his appetite was good.

On physical examination, the patient was obviously uncomfortable, looked tired and had lost some weight. There was definite tenderness in the midepigastrum. Examination of the meat-free stool showed the presence of occult blood. The gastric analysis showed a hyperacidity—72 and 94. The x-ray films revealed a tremendously irritable stomach with a filling defect in the cap. On Feb. 2 and 8, 1927, he was given 10 cc of a nonspecific milk preparation at each injection. Four days after the first injection, he was without symptoms, and he remained so up to the time this paper was written. The gastric analysis was 58 and 96. In the x-ray films the stomach was seen to be much less irritable, but the defect in the duodenum still remained. He had always been on a general diet and after he had regained the 8 pounds he lost prior to treatment, his weight had remained constant.

CASE 15—A man, aged 64, had had innumerable attacks of epigastric pain and discomfort for the past twenty years. The symptoms of which he complained in the present attack had been annoying for six months, and in the past two months he had been desperately uncomfortable with constant, gnawing pain. He had been on a soft diet for months and had lost a great deal of weight, his appetite was poor. During the first attacks the pain had been relieved by food or soda, but in more recent years this had been of no avail.

On physical examination, the man was found to be underweight, sick, tired and anemic. There was a mild generalized psoriasis and marked tenderness and spasm in the midepigastric region. Occult blood was presented in the stool, and x-ray films showed an irritable, dilated stomach with a large filling defect in the duodenum. The gastric analysis was 74 and 92.

On Jan. 2 and 9, 1928, he received 10 cc of a nonspecific milk preparation. The pain was entirely relieved in three days, and the discomfort due to gas was lessened. Two months later he was without symptoms, and he remained so for six months after treatment, although three months before this paper was written he had an attack of grip. Two months after treatment the gastric analysis was 60 and 70, and the x-ray films did not show any change. At that time he was on a general diet and had gained 14 pounds (6.4 Kg.). At the time this paper was written, the gastric analysis was 30 and 46 and the x-ray films still unchanged, although he looked like a new man.

CASE 16—A man, aged 43, complained of pain in the upper part of the stomach for six months. He had been told that he had an ulcer and was on a soft diet. The symptoms had been intensifying and food, which had relieved him in his three previous attacks during the past two years, was without avail. He had not lost weight, and his appetite had been bad for only two or three weeks.

The physical examination gave negative results except for tenderness in the midepigastric area. The stools did not contain blood, and the gastric analysis showed a free acid of 46 and total of 56. Roentgenogenic examination showed a large filling defect in the duodenum.

He was given a nonspecific milk preparation, 10 cc at each injection, on April 2, 9, 16, 20 and 24 and on May 1, 1928. At the end of treatment his condition was unchanged, the gastric analysis was 60 and 88, and the x-ray plates the same. He was operated on at the Johns Hopkins Hospital by Dr. Dean Lewis, and a large indurated but not unusual duodenal ulcer was found. A gastro-enterostomy gave him complete relief.

CASE 17.—A negro laborer, aged 43, complained of pain in the pit of his stomach which was at times relieved by food and at others made worse. Symptoms had been present for three or four weeks, and at times there had been retention and vomiting. Eighteen months before admission, he had a similar attack. At this time, an appendectomy completely relieved him.

On physical examination, he was found to be in good general condition. Nothing unusual was found except mild tenderness in the epigastrium and marked clapping. Occult blood was present in the stool, and the gastric analysis was 40 and 75. The x-ray report was ulcer in the duodenum with atonic stomach and partial obstruction.

He was given 10 cc of a nonspecific milk preparation on April 2, 9, 13, 16 and 19, 1928. At the time of the fourth injection the symptoms had completely disappeared, and the stools did not show any traces of blood. On the night of the first three injections, there had been considerable localized epigastric pain. On April 21, the gastric analysis was 10 and 30, the x-ray films were unchanged. Three weeks later, the gastric analysis was 20 and 52, one of the x-ray films showed the complete outline of the duodenum, but the stomach was still somewhat dilated. At the time this paper was written, he was clinically well and had been on a regular diet for two months.

CASE 18.—A man, aged 46, complained of symptoms of four weeks' duration, i. e., a gnawing pain on an empty stomach and sour eructation which at first were relieved by food, later, he was afraid to eat and gaseous distention became a prominent and uncomfortable complication. He had two previous and similar attacks.

The physical examination gave negative results. The gastric analysis was 90 and 112. The stools did not contain blood, and the x-ray films showed a filling defect in the duodenum and an irritable stomach. On June 4 and 11, 1927, he was given 10 cc of a nonspecific milk preparation. All symptoms disappeared after the first injection, and he remained clinically cured for thirteen months. He was at all times on a regular diet. A second x-ray film was not made.

CASE 19.—For six weeks a man, aged 26, had been having a boring pain in the epigastrium which often spread over the entire abdomen and was usually helped by food or soda. He slept well, and his appetite was good. In the previous four years, he had five similar attacks which lasted from four to six weeks.

Physical examination gave essentially negative results. The stools did not contain blood, and the gastric analysis was not done. The x-ray showed a large filling defect in the duodenum. A nonspecific milk preparation was given in 10 cc amounts on March 6, 10 and 15, 1927. Complete relief from symptoms was experienced after the second injection, and he remained cured clinically. He had always been on a regular diet.

CASE 20.—For four weeks a man, aged 42, had severe epigastric pain which was not relieved by a soft diet, antispasmodics and rest. In three previous attacks lasting from four to eight weeks each, his appetite had been good, and the pain had been temporarily relieved by food or soda. He was quite uncomfortable and wanted relief quickly.

On physical examination the man was found to be thin, undernourished, anemic and sickly, with bleeding hemorrhoids and spastic upper rectus muscles. There was marked tenderness over their region. The hemoglobin was 74 per cent (Sahli), gastric analysis 58 and 76, and the stool contained macroscopic blood. On the x-ray films, a large filling defect was seen in the duodenum. The stomach was tremendously irritable. Complete relief from symptoms was obtained after the third of the injections of a nonspecific milk preparation which were given, 10 cc at a time, on April 2, 5, 8, 15, 18 and 24, 1928. At the end of the course, the x-ray films were unchanged, the gastric analysis was 30 and 76, the hemorrhoids had been benefited by local treatment, he had gained 8 pounds and looked well. He was on a regular diet after the third injection. His cure was permanent up to the time this paper was written.

CASE 21—A man, aged 30, complained of a gnawing hunger pain in the epigastrium coming on two or three hours after meals and relieved by food or soda. The attack had lasted two weeks and was the fifth successive recurrence of attacks in the fall and spring. His appetite was good, and he had not lost weight.

Physical examination gave essentially negative results. The stool did not contain blood. The gastric analysis was 50 and 70. A filling defect in the duodenum was found in the x-ray films. He was kept on a general diet and given 10 cc of a nonspecific milk preparation on June 4, 10 and 16, 1927. Three days after the first injection all symptoms left, and he remained clinically well up to the time this paper was written. On July 6, 1928, the gastric analysis was 42 and 64 and the filling defect in the duodenum was much smaller according to the x-ray films.

CASE 22—A man, aged 30, badly crippled with arthritis, complained of a gnawing feeling in the pit of his stomach. It had been present off and on for six weeks and was at times temporarily relieved by food and at others made worse. More recently, there had been some nausea with retention vomiting at times.

A similar but less severe attack had occurred eighteen months before admission when the patient was in a naval hospital for treatment of the arthritis. There he received intravenous injections of mercurochrome-220 soluble and intramuscular injections of whole milk without benefit to the arthritis or the gastric discomfort. Since he had been under autogenous vaccine therapy, the arthritis had been greatly helped.

The physical examination showed generalized arthritis deformans, slight tenderness in the epigastrium and clapping. The gastric analysis was 42 and 62, and occult blood was found in the stool. X-ray films showed an irritable stomach and a filling defect in the duodenum. There was considerable six hour retention. Ten cubic centimeters of a nonspecific milk preparation was given May 2, 4, 7 and 10, 1928, and resulted in complete relief from symptoms as well as the gastric retention (as shown by the x-ray films). He was kept on a regular diet.

The patient also volunteered the information that his joints felt less stiff than previously.

CASE 23—A man, aged 45 had had symptoms for four weeks a gnawing, boring pain in the epigastrium more or less constant, usually temporarily relieved by food and accompanied by a great deal of gaseous eructation and distention. For three weeks he had been taking a soft diet antispasmodics and alkalis, without benefit. Four years before admission, he had a similar attack which lasted for two months.

Physical examination gave essentially negative results. The stools did not contain blood, and gastric analysis was 30 and 48. The x-ray films showed an irritable stomach with a filling defect in the duodenum. A nonspecific milk preparation (10 cc) was given May 4, 7, 10, 14 and 17, 1928. The pain stopped after the second injection, but the gaseous distention and eructation continued for three weeks. At that time the gastric analysis was 34 and 52 and the x-ray films unchanged. He was on a regular diet and when this paper was written was clinically well.

CASE 24—In the spring and autumn previous to admission, a man, aged 27, had attacks similar to the present one. This attack had been active for three weeks with boring hunger pains localized in the epigastric area, usually temporarily relieved by food. Medical treatment did not give any help, and the belching and regurgitation had become worse.

Physical examination gave essentially negative results. The stool did not contain blood, and the gastric analysis was 84 and 96. The x-ray films demonstrated a filling defect at the pylorus, with an irritable stomach. He received 10 cc of a nonspecific milk preparation on May 17, 21, 23 and 25, 1928, and returned home feeling greatly improved. Six weeks later he was in about the same condition. He was on a general diet.

#### SUMMARY

1 Intramuscular injections of a purified milk protein have been given to twenty-four patients suffering from peptic ulcer.

2 Of these patients, 83.2 per cent have been greatly improved or clinically cured.

(a) All of the patients were ambulatory.

(b) Pain was the first symptom to disappear.

(c) Other symptoms disappeared later.

(d) Ten cubic centimeters was given at each injection.

(e) There were two mild general reactions.

(f) A local reaction occurred in one patient.

(g) The majority of the patients were on a general diet.

3 There is no constant rise or fall in gastric acidity following treatment.

4 Great change is not demonstrated by x-ray examination, although spasm may be markedly decreased and the shadow defect appear smaller.

5 It is not suggested that this is a permanent cure. It has been used for too short a time and in too few cases.

6 The nature of the reaction produced by the milk protein is unknown.

# OPIUM ADDICTION

## II PHYSICAL CHARACTERISTICS AND PHYSICAL FITNESS OF ADDICTS DURING ADMINISTRATION OF MORPHINE<sup>\*</sup>

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Among the many problems present in connection with opium addiction is one about which there seems to be a good deal of controversy—Does addiction to this drug bring about physical deterioration? A good deal of confusion that exists in the literature on this subject is due, as Terry and Pellens<sup>1</sup> have pointed out, to variation in individual susceptibility and the amount of daily dosage and to the failure to distinguish between drug balance and early withdrawal symptoms

Opium addicts, when once “hooked,” as they so aptly express their plight, need a certain daily dosage to prevent the appearance of “withdrawal symptoms” In certain types of users, this dosage may remain constant in small quantities for years Another and far more numerous group is composed of those who increase the amount used until eventually they are forced to undergo treatment or begin reduction of the dose themselves In either event, they must endure some or all of the withdrawal symptoms which are practically always associated with loss of weight and, according to the addict extreme weakness

With this question in mind we have studied a series of patients who were addicted either to morphine or to heroin We believe that the underworld type, which constituted the greater percentage of our cases is the best group for this study as they have been subject to the various factors mentioned by Terry and Pellens<sup>1</sup> which have clouded the issue of physical deterioration and physical fitness Our studies consisted in measuring the weights heights and vital capacities making thorough physical examinations and subjecting the patients to Schneider’s test of physical fitness during the administration of a sufficient amount of morphine to supply their needs and comparing these observations with normal standards

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\* From the Narcotic Wards of the Philadelphia General Hospital

\* Expenses of this research were defrayed by the Committee on Drug Addictions, New York City The research was carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction in the wards of the Philadelphia General Hospital which were placed at our disposal through the courtesy of the Director of Public Health City of Philadelphia

1 Terry, Charles E and Pellens Mildred The Opium Problem, Camden, N J, Haddon Craftsmen 1925

## PHYSICAL EXAMINATION

A careful examination in ninety-six cases together with information gained from the supervision of the physical examination in 450 additional cases by the interns on service gave the following results

The large majority of the patients were between the ages of 20 and 40 and their physical status conformed closely to that of the normal persons of that age and group. Some showed emaciation which some-



Fig 1—Scar formation, the result of six months' hypodermic administration of heroin

times reached an extreme degree, but many were muscular and well developed and a number were obese

The skin was sallow in many cases, but this change in color was practically always present in patients who lived a rather unhygienic sedentary life. On the other hand, the skin of those who followed healthy outdoor occupations had the color of excellent health

Distribution of hair conformed to that of normal persons. A few showed premature grayness, but the incidence was not out of proportion to that for the general population

Sixty per cent of these ninety-six patients showed scars of previous abscesses, and 5 per cent had active abscesses on admission to the hospital. These were usually found over the upper arms, abdomen, thighs and buttocks. Several types of scars were noted. The older marks were pale bluish discolorations just below the skin which the patients declared were due to cocaine. The more recent marks were the result of abscesses caused by improperly disinfected hypodermic needles or by the irritating diluents used with either morphine or heroin, the average diameter of the abscesses was about 4 cm. The abscesses when healed left depressed, cicatrized scars. The subcutaneous tissue of the arms, thighs and abdomen was quite frequently the seat of a good deal

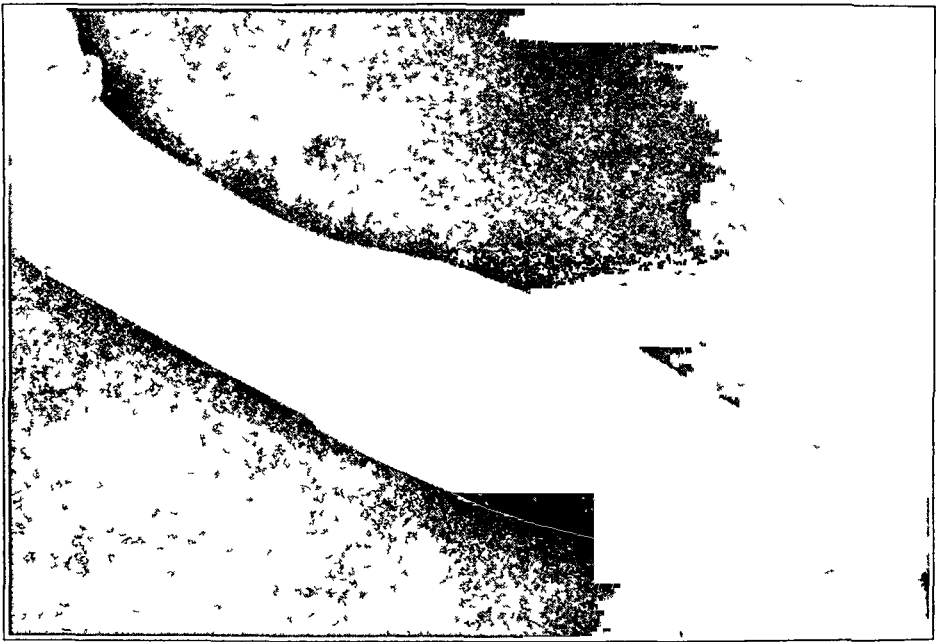


Fig 2—Points of injection with discoloration over superficial veins of forearm and arm, in addict using 20 grains (1.3 Gm.) of morphine intravenously daily for a period of six months.

of induration and often small, isolated, nodular masses could be palpated. We have seen one case of tetanus develop from suppurating abscesses.

The pupils were practically always contracted when the patient had had his usual quantity of the drug. They reacted to light and in accommodation, though somewhat more sluggishly than normally. In three patients (3.3 per cent) who had been addicted for periods of more than ten years, the contraction of the pupils was absent during administration of the drug. The extra-ocular movements were normal. The eyegrounds did not show any abnormality of either the retina or the vessels.

The nose rarely (2 per cent of our cases) presented a perforated septum as a result of the patient sniffing cocaine. In 40 per cent of our cases we encountered considerable congestion of the nose and nasopharynx with increased secretion and consequent difficulty in breathing through the nostrils.

Sixty per cent of the ninety-six patients examined exhibited a particularly high degree of pyorrhea and dental caries. Before attributing these changes to the continued use of drugs, one must bear in mind that these people are notorious in their lack of care of the teeth and



Fig. 3—Active abscesses, the result of two months' hypodermic injections of 70 grains (4.5 Gm.) of heroin daily by a fellow addict.

failure to consult a dentist. Two per cent had suppurating abscesses about the teeth. A tremor of the tongue was present in 4 per cent of the patients examined. Otherwise, the oral cavity showed nothing abnormal. The throat (40 per cent) showed a chronic inflammatory condition, but these persons are excessive smokers, a factor to be borne in mind.

The thyroid was not palpable in a single case. The chest was, as a rule, of normal shape with good expansion. In four cases inactive fibroid tuberculosis was present, which was confirmed by roentgen examination. The heart was normal in size as determined by percussion, and the apex beat was in the normal position. Thrills were not present.



on palpation in any case. Heart sounds were of good quality, and in only one case of the ninety-six was a systolic mitral murmur present, with no evidence of cardiac decompensation. The heart rate was slow in most cases, the average being 68 beats per minute. There was evidence of sclerosis of the peripheral vessels in only one patient, a man, aged 64, who had a degree of sclerosis consistent with his age. He had been using morphine for thirty-two years.

The abdomen was soft and enlargement of the liver or spleen was not noted, nor were we able to elicit any tenderness in the liver. Fecal masses were often palpable in the descending colon. The extremities were, as a rule, poorly developed, except in patients who performed manual labor or engaged in exercise, in such persons the extremities were proportionately developed. Definite tremor of the outstretched hands was encountered in 4 per cent of our cases. The degree of staining of the fingers due to cigaret smoking is extreme.

#### WEIGHTS AND VITAL CAPACITIES

*Methods*—One hundred men were examined for age, weight and height, and comparisons were made with figures considered normal by the Mutual Life Insurance Company of New York. An allowance of 5 pounds (2.3 Kg.) was made for the weight of clothing in the insurance weight tables. Vital capacities were determined in eighteen cases and were compared with Dreyer's table,<sup>2</sup> both actual weights and normal weights for height and age being used.

#### *Weights and Vital Capacities of Opium Addicts During the Administration of Morphine*

	Number of Cases Above Normal	Number of Cases Below Normal	Highest Value, per Cent	Lowest Value, per Cent	Average for Group, per Cent
Weight compared with normal weight for height and age	43	53	+35	-21	+ 0.2
Vital capacity compared with Dreyer's normal using observed weight					
Dreyer's class B	10	8	+22	-30	+ 2.6
Dreyer's class C	12	6	+32	-25	+ 9.6
Using subject's normal weight for height					
Dreyer's class B	10	8	+22	-17	+ 3.4
Dreyer's class C	15	3	+30	-11	+10.5

*Results*—Ten persons in the group of 100 studied, whose height and weight were measured, varied 20 per cent from the normal weight for the age and height, these ranged 35, 31, 29, 28, 26 and 21 per cent above and 25, 24, 24 and 24 per cent below. The average weight above normal in the forty-three cases above the mean normal was 18 pounds

<sup>2</sup> Dreyer, Georges, and Hanson, G. F. *The Assessment of Physical Fitness*, London, Cassell & Co., 1920, pp. 115.

(82 Kg), the average weight below normal in the fifty-three cases below the mean normal was 19 pounds (8.6 Kg). The average of the entire group of 100 cases was only 0.2 per cent above normal. The average length of addiction of the patients showing weights above the normal figures was 10.5 years, with an average daily dosage of either heroin or morphine of 21 grains (1.36 Gm). The average length of addiction of the persons with weights below normal was 9.5 years, with a daily consumption of 22 grains (1.4 Gm) of drugs.

Vital capacities in eighteen cases were compared with Dickey's classes, which are as follows:

- Class A Army and Navy personnel, and any person who has undergone prolonged training in either service independent of his ordinary vocation in life
  - Police force
  - Athletes and active sportsmen
  - University students (playing games)
  - Fire brigade
  - Blacksmiths and boilermakers
- Class B Professional classes (doctors, lawyers, etc.)
  - Business men
  - Railwaymen
  - High grade mechanics
  - Clerks, upper class
- Class C Tailors
  - Shopkeepers
  - Shoemakers
  - Printers
  - Potters
  - Clerks, lower class
  - Painters

Our subjects classified as to occupations according to their own statements, which of course are subject to question, were four chauffeurs, two bookbinders, one salesman, one farmer, one printer, one driving instructor, one draftsman, one foreman in a garage, one miner, one cook on a ship, one railroad employe, one brass finisher, one reporter and one unknown. They belong, therefore, in Dickey's classes B and C. No constant significant deviation from the normal was observed, the vital capacities, when they varied from the normal, tended to be high rather than low for classes B and C.

#### PHYSICAL FITNESS

Schneider's test<sup>3</sup> was applied thirty-one times on twenty-one subjects during the administration of morphine. The resulting scores range from 1 to 17. In seventeen of these subjects the scores range from 10 to 17.

<sup>3</sup> Schneider, Edward C. A Cardiovascular Rating as a Measure of Physical Fatigue and Efficiency, J. A. M. A. **74** 1507 (May 29) 1920.

The remaining four cases scored as follows one case, 9 points, the second case, 8 and 12, the third, 1 and 5 and the fourth case, 6, 4 and 11. A perfect score indicating the ideal physical fitness is 18 points.<sup>3</sup> The test is based on pulse rates taken while the patient is reclining and standing, a comparison of the two, changes in blood pressure while the patient is reclining and standing and the increase in heart rate after slight exercise as well as the speed of return to normal.

Our subjects all scored well in the various determinations necessary except for the change in pressure when they changed from the reclining to the standing posture, in practically all cases, there was a tendency to a fall rather than a rise in pressure. Schneider<sup>4</sup> attributed this in many cases to excessive cigaret smoking, which invariably is noted in our cases. The low score of only 1 point obtained in one of our cases was in a person who was extremely neurotic but who did not show evidence of organic disease. There is no correlation between the various scores and length of addiction, daily dosage and age. Schneider<sup>4</sup> considered a score below 9 points as indicative of organic disease or unhygienic living.

#### COMMENT AND LITERATURE

We have been unable to find in the literature any data on actual weights, heights, vital capacities and tests of physical fitness in the opium addict. The various statements made in reference to opium addiction and its effects on physical appearance and physical fitness apparently are based on limited inspection. Levinstein,<sup>4a</sup> Osler<sup>5</sup> and Lambert<sup>6</sup> agreed that the drug may be used for months before any signs of emaciation appear. Osler<sup>5</sup> and Lambert<sup>6</sup> also stated that some persons can use the drug for several years without showing emaciation. Kraepelin<sup>7</sup> called attention to the fact "of how little the symptoms of the disease may catch the eye." Bishop<sup>8</sup> advanced the theory "that the same power which locked up the opiate in the body also locked up the toxic products of tissue metabolism." According to Bishop,<sup>8</sup> if the addict

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4 Schneider, Edward C., and Truesdell, Dorothy. Daily Variations in Cardio-Vascular Conditions and a Physical Efficiency Rating, *Am J Physiol* **67** 193 (Dec.) 1923.

4a Levinstein, Edward. *Die Morphiumsucht*, tr. by Charles Harrer, 1878.

5 Osler, W. *The Principles and Practice of Medicine*, 1894, ed. 6, New York, D. Appleton & Company, 1905, pp. 1160.

6 Lambert, A., In *Nelson's Looseleaf Medicine*, New York, Thomas Nelson & Sons, 1920.

7 Kraepelin, Emil. *Lectures on Clinical Psychiatry*, tr. from ed. 2 (German) rev. and ed. by Thomas Johnstone, ed. 3, London, Bailliere, Tindall & Cox, 1913.

8 Bishop, Ernest S. *Narcotic Drug Problem*, New York, The Macmillan Company, 1920, p. 47.

maintains "good elimination" he will escape detection and not show any signs of physical deterioration for years. In the few recognized cases of opium addiction that have come to autopsy, whether the drug was being taken at the time of death or not, the pathologic changes found have been insignificant (Ball,<sup>9</sup> Anders and Musser,<sup>10</sup> and Allbutt<sup>11</sup>)

Bishop<sup>8</sup> and Morat<sup>12</sup> both stated that they found not only enlargement of the liver, but tenderness over this area during addiction. We have been unable to confirm this observation in any case in which morphine was being administered in sufficient quantities to prevent withdrawal symptoms. The contracted pupils are by far the most constant physical sign, as most observers state, and may justify one in considering the possibility of addiction.

We do not doubt the existence of the extreme cases of emaciation reported in the literature. It is inevitable that some users of opium will at a certain time in their lives reach this degree of physical impairment. Sooner or later, the great majority exhaust their funds, and it becomes a matter of either drugs or food. At this point they invariably purchase drugs. They tend then to resort to cures or to attempt themselves to reduce their dosage, with consequent withdrawal symptoms.

This point is best illustrated by one of our patients who immediately after his first treatment in our ward again began the use of the drug when discharged from the hospital. Within a period of two months, during which time he was unable to obtain a sufficient amount of the drug and sufficient food, he lost 30 pounds (13.6 Kg.). He then returned to our ward where the drug, in quantities sufficient to prevent withdrawal symptoms, and abundance of food were administered for several days before treatment was begun. He showed a rapid gain in weight in this short period before treatment.

There is a direct ratio between the decline in strength and weight and the number of times the addict curtails his food in order to get the drug. We agree with the statement of Bishop<sup>8</sup> that if the drug is used in sufficient amounts in relatively normal hygienic surroundings, the opium addict will escape detection for years and will not show any obvious physical deterioration or impaired physical fitness.

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9 Ball, B. Des lésions de la morphinomanie, et de la presence de la morphine dans les visceres, Encephale, 1887

10 Anders, J. M., and Musser, J. H. Practice of Medicine, Philadelphia, W. B. Saunders Co., 1920

11 Allbutt, Thomas C. A System of Medicine, London, The Macmillan Company, 1905

12 Morat, D. Le sang et les secretions au cours de la morphinomanie et de la desintoxication, Paris, G. Steinheil, 1911, p. 180

## CONCLUSIONS

We have been unable to detect any marked physical deterioration or impairment of physical fitness aside from the addiction per se in the series of cases of opium addiction studied during the administration of morphine

We believe that the existence of considerable emaciation in certain cases is caused by the unhygienic and impoverished life of the addict rather than by the direct effects of the drug

# THE VENTRICULAR ELECTROCARDIOGRAM

AN EXPERIMENTAL STUDY \*

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The experimental work on the ventricular electrocardiogram by Rothberger and Lewis and their co-workers, Wilson and Herrmann,<sup>1</sup> Smith,<sup>2</sup> and others, indicates that the principal divisions of the electrocardiogram, namely, the QRS complex and the T wave, may not be commonly or equally affected under abnormal conditions, and that this is because the QRS represents the excitation and the T wave the retreat of the process by virtue of which the contraction occurs. The practical value of the unequal response for differential diagnosis suggested an investigation of the curve of the ventricle from this angle and the report which follows is concerned with the nature of the disturbances required to affect the component portions of the ventricular electrocardiogram, in other words, the relation of the changes in the QRS (and in this connection also the associated question regarding arborization block was involved), the T wave and the RT period, to the injury or destruction of heart muscle. When coronary vessels are closed a close parallel between the changes in the muscle and the T wave of the electrocardiogram does not exist, although right and left ventricular effects are associated with opposing actions on the T wave.<sup>3</sup>

## METHOD

Forty experiments were performed on dogs under chloroform narcosis, section of the vagus nerves, artificial respiration and the heart exposed by removing the sternum. The heart muscle was destroyed by the injection of 95 per cent solution of alcohol. In some of the experiments, bundle branch block was induced in order to compare the effect of the injections with those in which conduction through the bundle was undisturbed. The electrocardiograms were taken with a vertical (R A -L L) and transverse (across

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\* From the Laboratory of Physiology, Faculty of Medicine, Paris

1 Wilson, F. N., and Herrmann, G. R. Bundle Branch Block and Arborization Block, *Arch Int Med* **26** 153 (Aug) 1920, An Experimental Study of Incomplete Bundle Branch Block and the Refractory Period of the Heart of the Dog, *Heart* **8** 229, 1921

2 Smith, F. M. Experimental Observations on the Atypical QRS Waves of the Electrocardiogram of the Dog, *Arch Int Med* **26** 205 (Aug) 1920

3 Otto, H. L. An Experimental Study of the Extracardial Nerves. IV The Coronary Arteries, *Heart* **3** 691 and 697, 1928, Ueber die Beziehungen der Accel. zur den Folgen der Unterbindung von Coronargefassen, *Arch f d ges Physiol* **37** 528, 1927

the thorax, and perpendicular to the axial) leads. The effect of making small variations in the line of the leading was also studied in many of the experiments. The electrodes employed were heavy copper pins, and the line of the leading could be varied without disturbing the primary lead by the insertion of other electrodes.

### RESULTS

Extensive destruction of the heart muscle in the dog can be made before it causes circulatory failure. The injection of an irritant like hypertonic saline solution into the muscle does not significantly alter the electrocardiogram. These were observations also made by Eppinger and Rothberger,<sup>4</sup> who first studied the effect of this type of injury to the heart. Therefore, the electrocardiographic changes which occur from injections of alcohol are solely due to the destruction of the muscle, irritation of the muscle playing no part. In this connection two further points of interest appeared, namely, that mechanical irritation of the ventricular muscle was also without effect on the electrocardiogram, and, the amount of injection which was usually necessary to affect the T wave permanently was considerably less than that required to affect the QRS. Contrasted to the T wave, this portion of the electrocardiogram was stable and did not give indication of the changes, i. e., the destruction of muscle, which had taken place within the myocardium.

### THE CHANGES IN THE T WAVE

The injection into the muscle of the right ventricle tended to cause negativity of the T wave and the ST fusion, although this was rarely pronounced, even when the injection of the right ventricle was extensive. This observation was also made by Eppinger and Rothberger.<sup>4</sup> Frequently an injection into the conus region or in the upper corner of the right ventricle on the right margin of the heart caused the temporary elevation of the T wave and RT fusion.<sup>5</sup> No portion of the right ventricle had a specific influence on the T wave. The effects of injection into the conus, apex, central and right upper portions were compared. The effect produced on the T wave was occasionally positive in one lead. Discordant effects could be made concordant, however, without affecting the direction of the QRS by altering the line of the leading (not its direction). This was also observed<sup>6</sup> with regard to the action of the accelerator nerves on the T wave.

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4 Eppinger, H, and Rothberger, C J. Zur Analyse des Elektrokardiograms, *Wien klin Wchnschr* **22** 1091, 1909.

5 By RT fusion is meant the peculiar form of electrocardiogram in which the T begins before the complete descent of the second limb of the spike R to the iso-electric line. ST fusion is the obverse form.

6 Otto, H L. An Experimental Study of the Extracardial Nerves. *I*, *Heart* **3** 691, 1928.

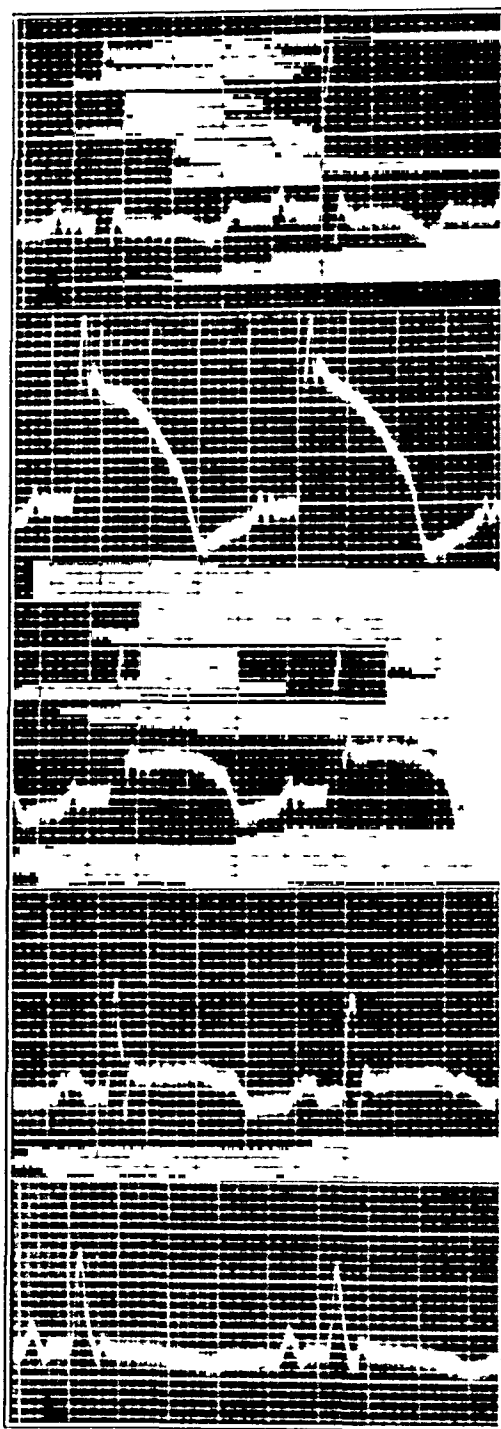


Fig 1—Axial (R A -L L) leading, time in fiftieth seconds *A* is the normal, *B*, *C* and *D* the changes which followed destruction of muscle in the left ventricle. The curves were taken immediately, five and ten minutes after the injury. *E* represents a permanent increase in the QRS time which followed destruction of muscle in the septum in the region of the left bundle. Note the final change in the RT interval from the injury to the left ventricular muscle (*D*)



Injection into any portion of the left ventricle caused the immediate appearance of the exaggerated RT fusion which Eppinger and Rothberger<sup>4</sup> reported. This was not a permanent effect, however, but receded in a few minutes to the original form of the electrocardiogram or to one which differed from it by the elevation of the RT interval above the iso-electric line, associated with an increase in the positivity of the T wave (fig 1). Since an irritation of the muscle from the injection will not explain the earlier effect, the latter must be the result of a transient, widespread paralysis of muscle function.

The degree of permanent change in the RT interval and T wave depended on the line of the leading as well as on the amount of muscle

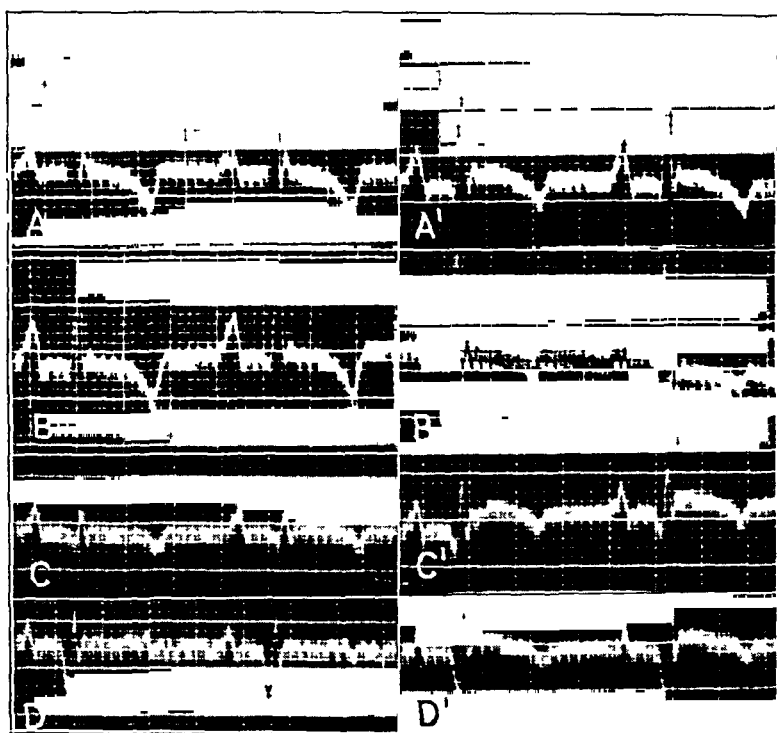


Fig 2—Time in fiftieth seconds, *A* is the axial (R A-L L) lead, *B*, transverse lead, *C*, transverse lead, with the right electrode placed higher in the wall of the right side of the chest, *D*, right electrode placed lower in the wall of the chest. *A'B'C'D'* indicate the alteration in the form and direction of the T wave after destruction of a small area of muscle in the wall of the left ventricle. Note how the line of the leading favors the appearance of RT fusion, *C'*.

destroyed by the injection, since small variations in the latter (often involving a change in the line of the leading not more than 30 degrees) altered the form and direction of the T wave or presented variations not observed in the other leads (figs 2 and 3).

A comparison of the effect of injection into the various portions of the left ventricle (the base, apex, papillary muscles and interpapillary regions) indicated that involvement at the basal portion of the

left ventricle did not induce enduring RT fusion, but that the injection into the apex or the interpapillary region frequently did so, and that the area of muscle destroyed which most uniformly yielded this effect was the interpapillary area and the adjoining portions of the bases of both papillary muscles. Sometimes only a small area of injection in this location was necessary to induce the RT fusion, one which did not destroy the entire thickness of the wall or involve the endocardium. The second branch from the circumflex division of the left coronary artery usually supplies this portion of the left ventricle, and

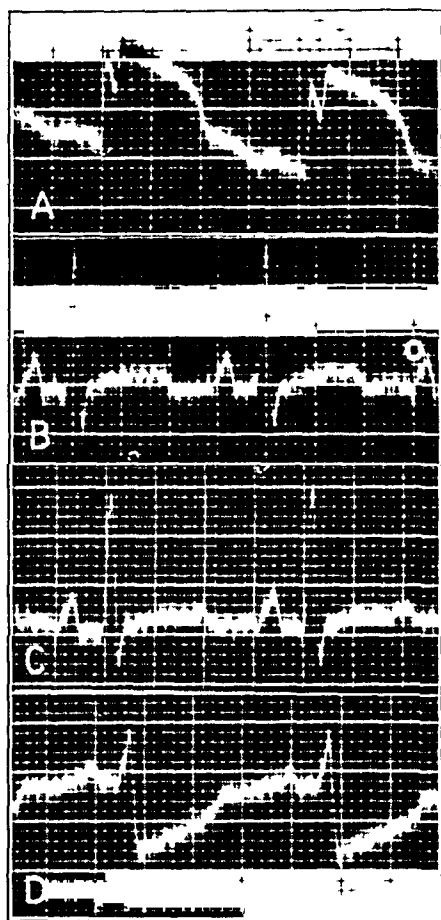


Fig 3—Time in fiftieth seconds. *A, B, C* and *D* are the same lines of leading as in figure 2. This electrocardiogram was taken immediately after the injection into an area of muscle at the upper right corner of the right ventricle. Note the differences in the recorded effect when the line of leading is altered.

the frequency with which this electrocardiogram was found to occur after the ligation of this vessel<sup>3</sup> confirms the observation.

Stimulation of the left accelerator nerve increased the RT fusion, whereas the stimulation of the right nerve lessened it, causing the descending limb of the R spike to descend closer to the base line before the beginning of the T wave associated with a diminution in the height of the T, from which it may be inferred that the action of the accelerator

nerves on the T wave of the electrocardiogram is not altered in the presence of myocardial injury or an abnormal type of electrocardiographic curve<sup>7</sup>

The line of the leading was also one of the conditions of importance in favoring the appearance of this form of electrocardiogram when other conditions were predisposed to it (figs 2 and 3)

Greatly disturbing the heart by inserting a small knife into the left ventricle and injuring the septum caused it to disappear from the axial lead (its appearance in other lines of lead was not investigated) The R wave then descended to the base line or below it before the beginning of the T wave These observations suggest that its appearance depends on a particular balance or sequence in the order of excitation and retreat in the myocardium

Injection into the septum was tested in six dogs, but the effect of the destruction of the muscle of the septum was not satisfactory, bundle branch block was the constant result of the injection whenever a large area of the muscle of the septum became involved

#### THE CHANGES IN THE QRS

*Voltage and Notching*—Although the extensive destruction of the muscle of the myocardium was frequently associated with a diminution in the voltage of the QRS, it occurred as a rule with notching However, primary diminution in the voltage can occur from a great decrease in the volume of active muscle Diminution in the voltage followed the extensive destruction of the heart muscle when bundle branch block was present, and also, under the same conditions, there was diminution in the voltage of premature beats elicited from the conus region without a change in their form But the amount of muscle which it was necessary to destroy in order to affect significantly the voltage of the electrocardiogram was too extensive to justify the deduction that this can be a cause of a low voltage when it is present in the human electrocardiogram The conclusion was inevitable that the actual amount of gross injury a heart sustained up to the point of causing the failure of its function is a factor of minor importance in the determination of the voltage of its electrocardiogram The common experimental association of an excellent voltage and cardiac beating so feeble that it is barely visible is also indicative of the same conclusion (fig 4)

The appearance of notching in association with the diminished voltage indicates that frequent and rapid changes in the position of the electrical axis of the heart are occurring<sup>1</sup> This is the effect anticipated from the destruction of large or scattered areas in the myocardium However, the inference from an electrocardiogram presenting notching

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7 This is also the case when coronary vessels are ligated

that the changes in the electrical axis are the effect of changes occurring in the heart muscle is hardly justifiable until it is certain that an altered position of the heart with reference to the leads is not responsible for it.<sup>8</sup> Figure 5 illustrates the appearance of a complicated notching in the transverse lead obtained by a slight alteration in the line of the leading, and figure 6 is one in which the line of leading is unchanged but the position of the heart is altered. The conditions surrounding the appearance of notching were unrelated to the QRS time.

*Alteration of the Direction of the QRS*—A great diminution in the functioning muscle of the ventricles did not vary the principal direction

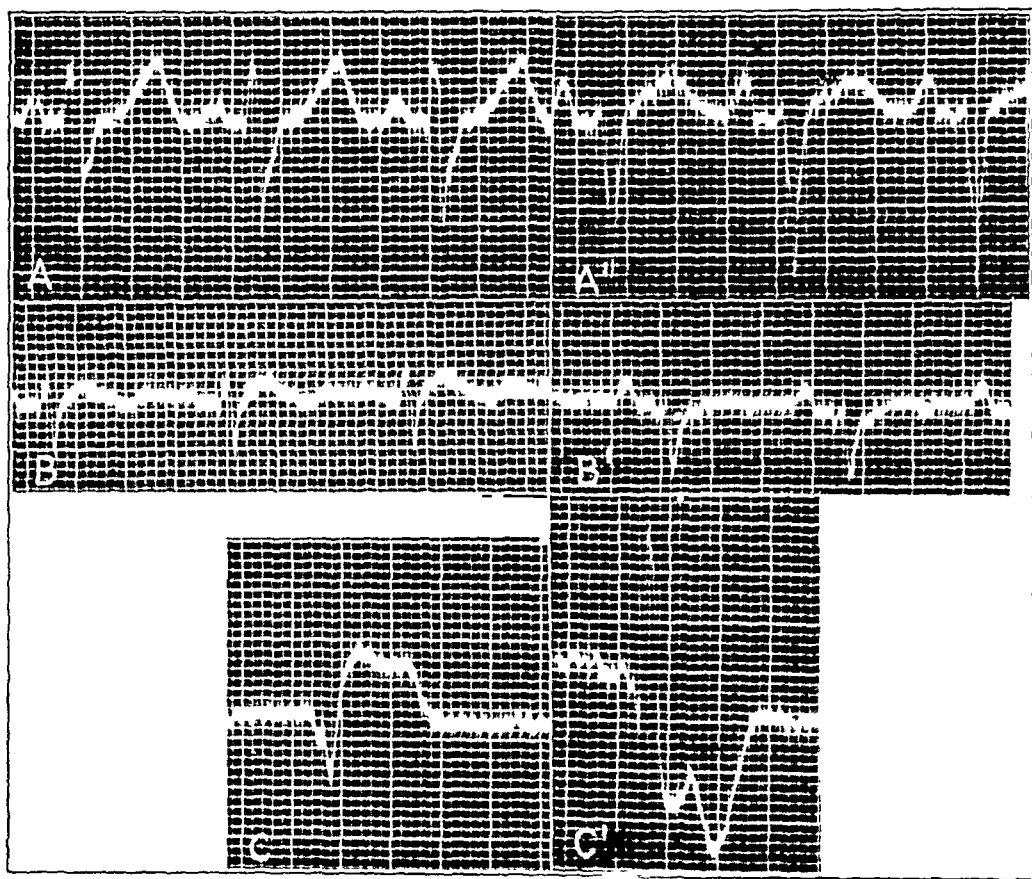


Fig 4—Time in fiftieth seconds. The right branch of the bundle has been cut. A is the axial lead, A', the transverse lead, B and B' are these leads after the destruction of practically all the muscle of the external wall of the right ventricle. Note the diminished voltage and QRS time. C and C' are these leads after destruction of muscle in the left ventricle and circulatory failure. The voltage is greater than when the heart was beating with good force and maintaining the circulation.

8 It is to be noted in passing that another cause of notching exists, namely, an altered conduction order through the branches of the bundle. The section of one of the main divisions of the left branch of the bundle of His, for example, may produce notching in either the transverse or the axial lead when it does not alter the direction of the QRS (fig 9).

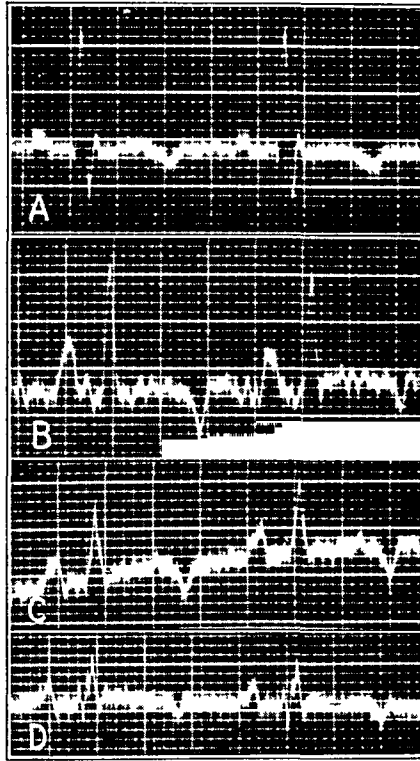


Fig 5—Time in fiftieth seconds *A B, C* and *D* show the same lines of leading as in figure 2 Complicated splintering with diminished voltage dependent on the line of the lead

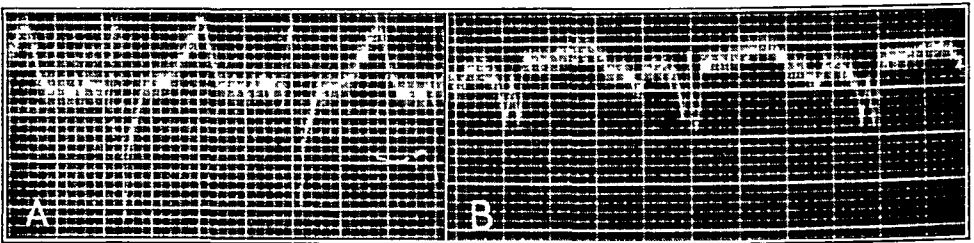


Fig 6—Time in fiftieth seconds, axial leading The right branch of the bundle has been cut, and the second figure shows the effect of altering the position of the heart with reference to the line of the leading The cardiac apex was tilted upward and to the right (The equivalent of a counter-clockwise rotation on the transverse axis of the heart )

taken by the curve. This receives confirmation in the effects obtained when coronary vessels are ligated,<sup>9</sup> whereupon large areas of muscle are thrown out of function without influencing the direction of the QRS. In this connection it is of interest to note that although the ratio between the weights of the right and left ventricles of the dog (excluding the septum) presents considerable variation which follows the weight of the dog,<sup>10</sup> the direction of the QRS is always upright. It is probable that "preponderance" curves when they do not involve an alteration in the position of the heart with reference to the leads must be explained on the basis of the excitation order within the heart without regard to the masses of muscle involved.

*The QRS Time*—As already mentioned, the only significant effect of injection into the muscle of the septum was the appearance of a bundle branch block. Since the injections into the outer walls of the right or left ventricles never resulted in bundle branch block or an increase in the QRS time, it could only be the effect of an injury to the bundle or its branches and not the muscle of the septum. This was further tested in six experiments by making an extensive injection around the points at which the main branches of the bundle reach the external walls of the ventricles, namely, the central region of the right ventricle, the papillary muscles, the junction of the left ventricular wall and the septum at its upper and middle thirds. In one of three animals into which an injection was made into the central region an increase in the width of the QRS with a form resembling that of right bundle branch block occurred after several of the injections, which endured after each injection for a few minutes only before the QRS time was again normal (fig 7), but the widest possible injection which did not involve the septum would not induce a permanent increase in the QRS time in any of the experiments. To the contrary, a distinct tendency exists for the QRS time to be diminished after the extensive destruction of the myocardium (fig 4).

In figure 7,f, the small QRS time after the section of the right bundle followed by a decisive increase when one of the divisions of the left bundle has been severed suggests that the right bundle has not been completely severed in this instance. This, however, was not the case because the postmortem examination showed that the right branch was completely severed. The peculiar form of electrocardiogram which this illustration reveals, the appearance of a QRS

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<sup>9</sup> Lewis, T. The Experimental Production of Paroxysmal Tachycardia and the Effects of Ligation of the Coronary Arteries, *Heart* **1** 98, 1909. Smith, F. M. The Ligation of Coronary Arteries with Electrocardiographic Study, *Arch Int Med* **22** 8 (July) 1918. Otto (footnote 3).

<sup>10</sup> In the lighter dogs it inclines toward equality, and in heavy dogs it greatly favors the left ventricle.

time less than is expected with right branch block associated with a QRS wave downwardly directed, the last stroke of which fuses without clear demarcation into a markedly positive T wave, was the characteristic curve in the axial lead when the combination of right branch block and the changes giving rise to the RT fusion were present

#### ARBORIZATION BLOCK

In 1917, Oppenheimer and Rothschild<sup>11</sup> described a type of abnormal electrocardiogram which they called arborization block because the hearts which gave this curve presented a patchy sclerosis involving the subendocardial muscle and Purkinje tissues when they were examined post mortem. The specific electrocardiographic criteria for the recognition of the condition were widening, notching and low voltage of the QRS, with the absence of the diphasic curves and the huge T wave,

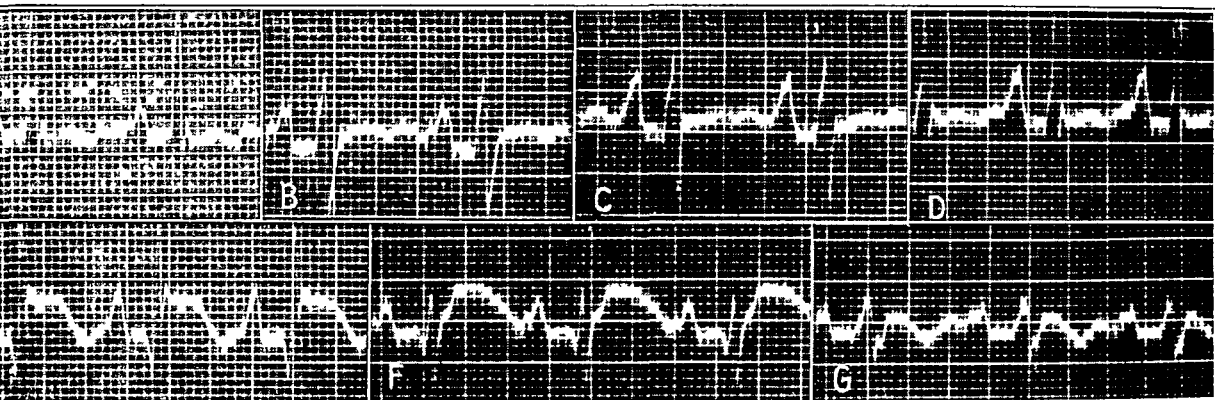


Fig 7—Time in fiftieth seconds, axial leading, *A* is the normal, *B*, immediately after extensive destruction of the muscle in the central region. The QRS is widened, the curve suggests the presence of right branch block. *C*, recovery to the normal QRS time, *D*, recovery of the original QRS form, slight splintering and an insignificant change in the T have occurred, *E*, after extensive destruction of the muscle of the left ventricle (the base of the papillary muscles and the area at the junction of the septum and left ventricle at its middle third), *F*, after section of the right branch of the bundle (note the appearance of a normal QRS time), *G*, section of one of the principal divisions of the left branch of the bundle

opposite in its direction to the main deflection, which are seen with experimental branch block

That an electrocardiogram like this, however, may be persistently present without finding the pathologic process described to account for it has been pointed out by Drury<sup>12</sup>. Experimentally, Wilson and Herr-

11 Oppenheimer, B. S., and Rothschild, M. A. Electrocardiographic Changes Associated with Myocardial Involvement, *J. A. M. A.* 69:429 (Aug 11) 1917

12 Drury, A. N. Arborization Block, *Heart* 8:23 1921

mann were unable to obtain curves resembling these by the section of the minor subdivisions of the branches of the bundle of His, nor at any stage of the transition between the normal complex and complete bundle branch block, Smith<sup>13</sup> caused extensive injury with fibrosis of the heart involving the endocardium without being successful in reproducing this type of electrocardiogram. Sherf<sup>14</sup> observed electrocardiographic forms resembling arborization block in badly damaged hearts at certain stages of the transition complexes when serial premature beats induced from the external walls of the ventricles were interfering with beats supraventricular in origin, and he concluded that arborization block was due to an incomplete block in one of the branches of the bundle associated with injury to the smaller divisions of the other branch of the bundle.

The most significant of the electrocardiographic criteria for arborization block is the increase of the QRS time. This could not be experimentally obtained by the section of the minor subdivisions of the branches of the bundle by Wilson and Heilmann,<sup>1</sup> nor by Rothberger and Winterberg,<sup>15</sup> although the latter investigators studied the effect of section of the principal branches of the bundle of His in great detail. Smith<sup>16</sup> was not more successful in obtaining it as the result of wide injury to the endocardium. In the comparison of the effect of section of the subdivisions of the branches of the bundle in a series of twenty-eight experiments I observed that a significant increase in the QRS time never occurred unless complete section of the bundle or all of its subdivisions to one of the ventricles was present, which is in accord with the observations of the previous investigators on the subject. Since the Purkinje network is no longer continuously available for the excitation only when a complete section of one of the two divisions of the bundle has occurred the increase in the QRS is the expression of the extra time required for the excitation to travel through the slower conducting heart muscle of the septum. On the other hand, destruction of the muscle or the endocardium which contains the Purkinje network to the point of circulatory failure will not induce an increase in the QRS time unless it involves an extensive injury to the septum in the region in which the primary branches of the bundle are known to pass, or an injury to all of the bundle of His which supplies one ventricle, or, as suggested by Smith, unless it is associated with myocardial fatigue, under which circumstances all

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13 Smith (footnote 9, second reference)

14 Sherf, D. Zur Entstehungsweise der Extrasystolen und der extrasystolischen Allorhythmien, *Ztschr f d ges exper Med* **51** 816, 1926

15 Rothberger, C. J., and Winterberg, H. Exper Beiträge zur Kenntnis der Reizleitungsstörungen, usw., *Ztschr f d ges exper Med* **17** 264, 1916

16 Smith (footnote 2, and footnote 9, second reference)



conduction, both in Purkinje tissue and in ordinary heart muscle is in all probability also slowed. The experimental evidence makes it reasonably certain that a significant widening of the QRS does not ordinarily appear except by the complete elimination of one branch of the bundle, and this becomes the more unlikely to occur as the branch in question progresses in its subdivision. Suggestive in this connection is the early subdivision of the left bundle and the rarity with which left bundle branch block is seen in the clinic, and the comparative difficulty with which left bundle branch block is experimentally produced in the dog. When an arborization block curve is present, the presence of a complete bundle branch block must be assumed in order to account for the abnormal width of the QRS.

Notching, as Wilson and Herrmann<sup>1</sup> have pointed out, represents the occurrence of frequent and rapid changes in the position of the electrical axis of the heart and is greatest in the lead with the lowest voltage. These criteria therefore will appear together. They can be experimentally produced in the electrocardiogram of the undisturbed heart by shifting the line of the leading into a position which presumably favors a frequent change in the electrical axis with reference to the line of the leading (figs 5 and 6). Under these conditions, the notching becomes especially pronounced in the presence of the section of one of the two divisions of the left bundle and the complete section of the right bundle. This makes the excitation issue to the ventricle through one strand of the bundle instead of three, and an exaggeration of the effect may be expected since changes in the electrical axis are also exaggerated, and the wide QRS facilitates the clear inscription of the notching (fig 9).

The differences in the T wave in arborization block and bundle branch block do not appear to be an important differential criterion when it is remembered that the T wave is also greatly diminished in size in a lead which yields low amplitude with notching and that a small alteration in the line of the lead will often alter its direction entirely without affecting that of the QRS.

Figures 7, 8 and 9 are curves obtained by sectioning the right branch of the bundle and of one of the divisions of the left branch.

It is suggested that the electrocardiogram which is termed arborization block is a bundle branch block involving the entire right bundle and part of the left bundle associated with a change in the position of the heart probably a postero-anterior rotation, i. e., rotation on the transverse axis of the base. The effect of this type of alteration in the position of the heart, it has been suggested elsewhere,<sup>17</sup> is to cause a diminished voltage in all leads.

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17 Otto, H. L. The Effect of Altering the Position of the Heart upon the Electrocardiogram, *Proc Soc Exper Biol & Med* 26:4218 1928-1929.

An increased QRS time can result from destruction of the muscle of the septum when the latter completely involves at least one branch of the bundle. The injury which does this may be grossly in evidence as in the case of obstruction to a coronary artery, or it may be chronic and widely diffused as with arteriosclerotic conditions or finally, localized, minute and undetectable as in most instances of bundle branch block. It is evident that a specific pathologic process cannot be associated with an electrocardiogram which tests

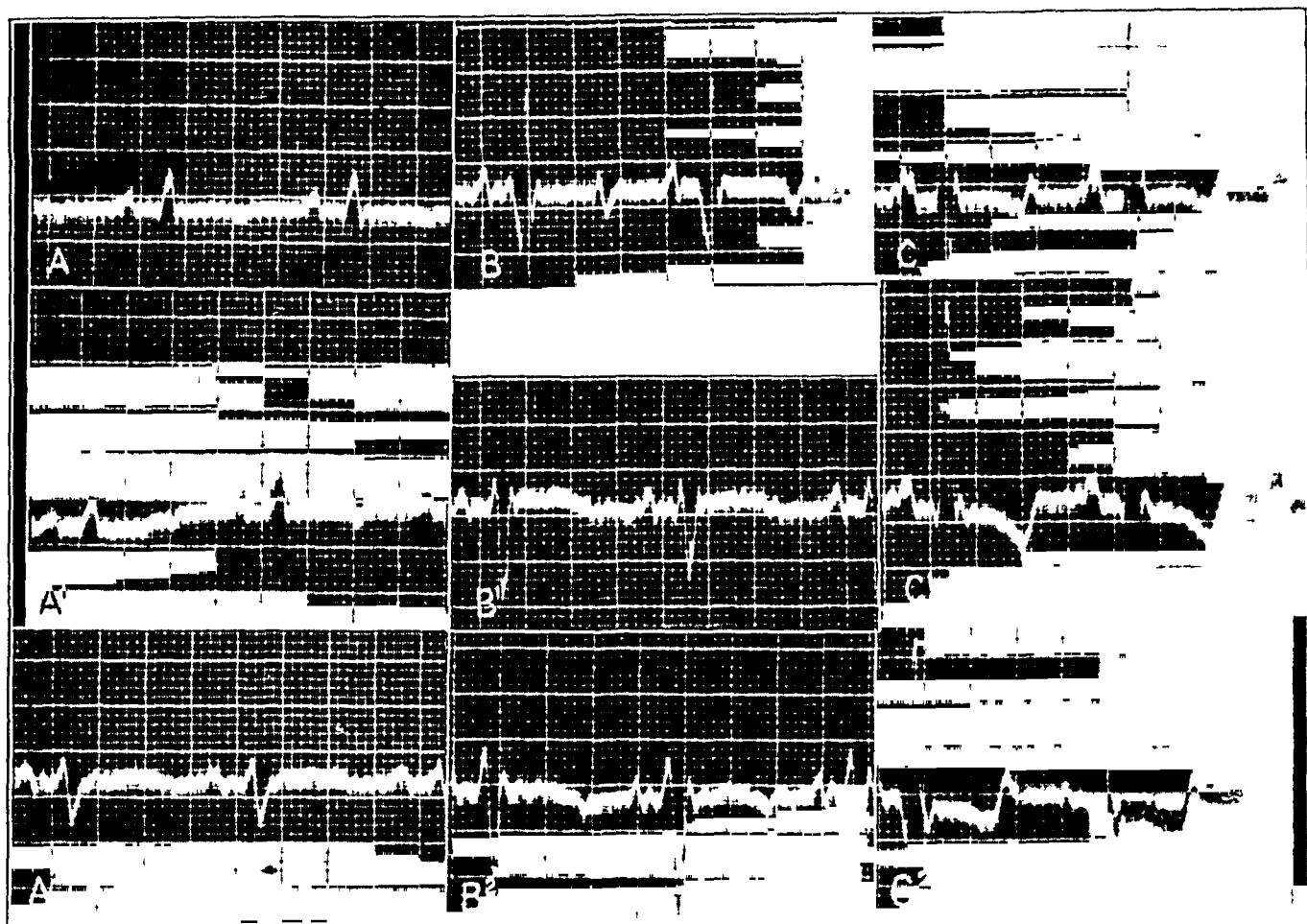


Fig 8—Time in fiftieth seconds, A-R A-L A (corresponding to derivation I) B is the transverse lead across the thorax, C, the axial lead A', B' and C' are the same after section of the posterior division of the left branch of the bundle. The QRS changes in form although a normal QRS time persists A'', B'' and C'' show these leads after section of the right branch of the bundle. Discordant bundle branch block curves are present (with only one branch of the bundle sectioned they are practically always concordant). Note the absence of the other characteristic features of uncomplicated monolateral bundle branch block.

on special conditions of conduction and relations to the plane of the leading. That it is frequently associated with an old infarct from the closure of the descending division of the left coronary artery is readily

understood since this branch extensively supplies the muscle of the septum in the region traversed both by the right bundle before it begins its subdivision and by the anterior division of the left bundle

#### COMMENT

The T wave is the more sensitive index of the changes which occur within the myocardium. To affect permanently the T wave the amount of tissue destroyed was much less than that necessary to affect the QRS. Whether this difference is grounded in the difference in the physiologic processes which these portions of the curve represent, or is merely due to the fact that the slow inscription of T gives evidences of change which are hidden by the rapid movement of the string when the QRS is written is beyond the scope of the observations.

The most constant effect on the electrocardiogram caused by the destruction of heart muscle was the shift of the RT interval from the iso-electric line, which is experimental evidence for the importance

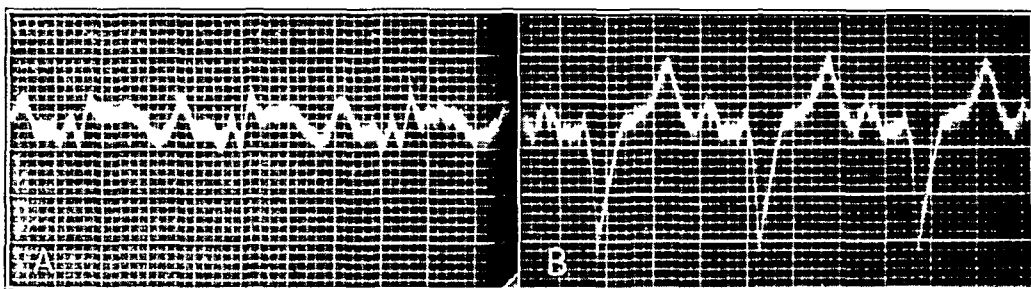


Fig 9—Time in fiftieth seconds, complete section of the right branch of the bundle, section of the anterior division of the left branch with some injury to the remaining division of the left bundle. *A'* is the transverse lead (in this animal the R A-L A lead gave a similar curve), *B*, the axial lead. There is marked notching in the transverse lead, and the QRS is abnormally wide (the dog weighed 25 Kg). This is again a discordant curve, but the reversal of the discordance of figure 8.

with which this change is regarded clinically. No value could be attached to any of the other changes in the RT period associated with it and the form of the T wave, when the distinctive ST and RT fusions (which are exaggerations of this shift of the RT portion of the curve from the iso-electric line) are disregarded, did not appear to hold a position of importance.

The destruction of the muscle of the right ventricle tended to cause negativity of the T wave in contrast to destruction of the muscle of the left ventricle, which caused positivity of the T. This relation of the two halves of the heart, the right and upper versus the left and lower portions, to the T wave of the electrocardiogram is further substantiated by the effect of ligation of coronary arteries,<sup>3</sup> and the

effects obtained when cooling the heart muscle is compared to freezing it<sup>18</sup> But the ease with which an altered line of leading alters the direction of the T wave when comparatively small areas of muscle are destroyed make it doubtful if the direction assumed by the T wave when injury is known to be present may be used to infer the location of the injury It suggests, however, that in searching for evidence of injury to the heart as indicated by alterations in the T wave it might be of aid to have recourse to leads from the chest and to observe the curve through several lines of lead, compassing more cardiac diameters than the leads from the points of Einthoven triangle These are all within the one plane

Since an irritation of the myocardium does not have an effect on the form of the electrocardiogram, it may be assumed that inflammatory conditions of the epicardium or myocardium which do not involve the conduction system or inhibit the functioning of the muscle are without effect on the form of the curve and significant alterations of the curve, excluding the action of the extracardial nerves, are probably indicative of depressive or destructive processes

A substantial increase in the QRS time was unassociated with the destruction of the ordinary heart muscle or the endocardium, which contains the Purkinje network, but was constantly related only to involvement of an entire branch of the bundle or all of its subdivisions to one or the other of the ventricles Since significant QRS widening does not occur if a subdivision of a branch of the bundle remains to supply the ventricle in question its presence may be taken as good evidence of injury which completely involves one of the branches of the bundle Furthermore, to associate a wide QRS time with injury to the cardiac septum appears to be a justifiable deduction from the experimental observations The effects on the QRS time which are toxic and are obtained by the exhibition of drugs like cocaine or quinine, or are endogenous (cardiac fatigue<sup>2</sup>), are not contrary evidence but represent a group of special conditions in which there is no distinction between conduction effects in the ordinary heart muscle and Purkinje tissues

The tendency toward diminution in the QRS time from extensive destruction of the muscle in the presence of a bundle branch block suggests that initially it is the volume of the heart muscle in function and the thickness of the septum which determines the width of the QRS complex (when other conditions such as conduction changes do not alter it) Suggestive in this connection is the average width of the QRS time in the presence of a right bundle branch block in the cat, the dog and the human being In the first, it is usually under 0.05 seconds, and in the dog it varies between 0.06 and 0.08 seconds,

whereas in man 0.12 seconds is the accepted minimum QRS time for bundle branch block. The abnormally wide QRS time in many greatly hypertrophied hearts may perhaps be explained in this way.

Since an altered position of the heart with reference to the leads as well as altered conduction order within the heart may cause notching, inferences from it concerning the muscle must be made with circumspection.

Finally, the term intraventricular block which is employed when an abnormal width of the QRS is present is more properly designated interventricular block. It represents a bundle branch block which, if partial, can be so only in a temporal sense, i.e., a delayed conduction through one branch of the bundle, not the effect of injury to some of its branchings. Intraventricular block should be the term reserved for instances in which a toxic prolongation of conduction diffused through the heart muscle is present.

#### SUMMARY AND CONCLUSIONS

1 Destruction of heart muscle causes a shift of the RT period of the electrocardiogram from the iso-electric line, and the degree to which this alteration occurs is closely related to the line of the leading as well as to the injury to the muscle.

2 The extensive destruction of heart muscle does not have a significant effect on the QRS complex of the electrocardiogram when the principal divisions of the His bundle are unaffected. An increase in the QRS time is obtained only when all of the bundle to one or the other ventricle is affected.

3 Arborization block represents a complex form of bundle branch block, involving all of the right branch and part of the left and associated with an altered position of the electrical axis with reference to the plane of the leading.

4 What is called intraventricular block is more properly termed interventricular, because the latter better defines the conditions of impulse conduction which underlie the appearance of this form of electrocardiogram.

# CHRONIC PULMONARY INFECTION DUE TO THE FRIEDLANDER BACILLUS

A CLINICAL AND ROENTGENOLOGIC STUDY<sup>1</sup>

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Friedlander's pneumonia is an acute pulmonary infection, usually fatal, caused by *Bacillus mucosus-capsulatus* and characterized particularly by a viscid, bloody sputum and lobular involvement of the lung parenchyma with a marked tendency to the formation of secondary multiple abscesses.

In 1882, Friedlander described a "micrococcus" which he took to be the cause of lobar pneumonia. However, after Frankel and Weichselbaum had shown in 1886 that the pneumococcus was the causative organism in most cases of acute lobar pneumonia, it was found that the so-called "micrococcus" of Friedlander was in reality a short, gram-negative bacillus. This bacillus occurs either as a primary or a secondary invader in about 5 or 10 per cent of all cases of acute lobar pneumonia.

## BACTERIOLOGY

The bacillus of Friedlander varies greatly in size and morphology. Usually it is short and rather broad, with rounded ends. Its length varies from 0.6 to 5 microns and its width from 0.5 to 1.5 microns. The short, thick forms are almost coccoid in appearance, which probably accounts for the fact that Friedlander originally called this organism a "micrococcus" rather than a bacillus. They are nonmotile, do not form spores and are surrounded by a capsule.

## PATHOLOGY

There are certain outstanding features in the pathologic structure produced by the Friedlander bacillus. At autopsy the involved area appears to be lobar in type, but on section, multiple small intervening areas of normal lung tissue show that the process is, in reality, a marked confluent lobular pneumonia or bronchopneumonia. Pleurisy may be a prominent feature. Over the affected area, the visceral and

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<sup>1</sup> Submitted for publication, Nov. 1, 1928.

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parietal pleura may be densely adherent. The affected lung appears larger than normal, and when it is cut there is an abundant, viscid, bloody exudate. The cut surface is mahogany brown, with marble-like streaking. It is the rule for multiple abscesses to be found, these varying greatly in size. The walls of these abscesses are usually smooth and quite thin. In them is found the same type of exudate that is found on the cut surface of the lung. Between the cavities are seen irregular areas of air containing tissue. Relatively little fibrin is seen on the cut surface.

Microscopic examination shows the alveoli filled with an exudate composed of polymorphonuclear leukocytes, alveolar epithelium and degenerated lymphocytes. Some fibrin is seen, but it is much smaller in amount than that found in the pneumonia produced by the pneumococcus.

#### REVIEW OF THE LITERATURE

Concerning the clinical course of Friedlander's pneumonia, there is relatively little in the literature. In 1915, Sisson and Thompson<sup>1</sup> reviewed thirty-three fatal cases from the literature, some of which were open to question as unequivocal cases of Friedlander's pneumonia. They reported, in addition, four new cases, all of which were fatal.

In 1919, Zander<sup>2</sup> described an epidemic of Friedlander's pneumonia in Germany. Between December, 1916, and March, 1917, there were 411 cases with 144 deaths. The highest mortality occurred in the age groups of 30 to 40 and 40 to 50, being higher in the latter. In this epidemic, chills occurred at the onset in 118 cases, or 28 per cent. In the majority of the cases, the illness started in the lower lobes. In a large percentage of the cases the first examination showed that more than one lobe was involved. The extremes for the duration of fever were 2 and 48 days. The average was 9.5 days. In 131 cases (31 per cent) fever fell by crisis and in 127 (30 per cent) by lysis. In these cases the clinical observation was made that in the beginning, the picture was apt to be that of croupous pneumonia but later the picture became more that of bronchopneumonia.

Eighteen additional cases were reported by Belk,<sup>3</sup> of the Philadelphia General Hospital, in 1926, all of which had been fatal. Three of these cases had been considered chronic forms of pulmonary tuberculosis during life.

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1 Sisson and Thompson. Report of Thirty-seven Cases, *Am J M Sc* **150** 713, 1915.

2 Zander. *Deutsche med Wchnschr* **45** 1180, 1919.

3 Belk, W. P. *J Infec Dis* **38** 115 (Feb) 1926.

An instructive case of Friedlander's pneumonia was reported by Nils Westermarck<sup>4</sup> in 1926. His patient's illness started acutely with a chill which was followed two days later by pain in the left side of the chest. There were cyanosis, reddish sputum and bilateral physical signs in the chest. A diagnosis of bronchopneumonia was made. After a time the patient improved and was able to leave the hospital, but was readmitted six months later, at this time x-ray examination of the chest showed bilateral cavities in the upper lobes and changes in the lower lobes apparently due to fibrosis. The entire pathologic process was considered to be tuberculous, although tubercle bacilli had never been demonstrated. The patient died a month later. At necropsy multiple abscesses with rather a thin wall were found, and Friedlander's bacilli in great numbers were recovered from the contents of the cavities of the abscesses. Tubercle bacilli were not found. The record of one of our patients (case 2) resembles this case in several respects.

#### CLINICAL COURSE

The clinical course of Friedlander's pneumonia is variable. It occurs most frequently in the late years of adult life. Only one case, to date, has been reported during infancy or childhood. As in the case of acute lobar pneumonia, alcohol seems to be an outstanding predisposing factor. The onset may be similar to that of pneumococcic pneumonia. In fact, the case at first may be regarded as one of the usual lobar pneumonia. Hemoptysis is a common early symptom. The symptoms may come on with great violence accompanied by high fever, chill and prostration. Cyanosis may be a prominent symptom. The patient usually expectorates large amounts of viscid reddish sputum, and some writers regard this feature as being almost pathognomonic. In this sputum, the Friedlander bacilli are readily found in large numbers. In severe cases the prostration increases, the cyanosis becomes more marked and is combined with a dusky red coloration of the skin, and in the first twenty-four or forty-eight hours, death ensues.

On the other hand, the course of the disease may be quite prolonged or may become chronic. During the past year, we have had the opportunity of studying three such cases. It is our belief that cases of this kind give rise to a chronic form of Friedlander infection which we have come to regard as quite analogous to chronic pulmonary tuberculosis, as acute exacerbations may occur at any time. In our study of these cases we have been greatly aided by the roentgen-ray examination. By means of serial roentgenography, we have been able to follow the development of the pathologic condition from the onset of the disease to the establishment of the chronic stage.

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<sup>4</sup> Westermarck, N. Pneumonia with Friedlander's Bacillus Simulating Tuberculosis, Case, *Acta Radiol.* 7:626, 1926.



## ROENTGEN-RAY ASPECTS

The literature concerning the roentgen-ray aspects of Friedlander's pneumonia is extremely meager. Our knowledge of the roentgenologic appearance is based on a study of the underlying pathologic condition. We recognize the onset of the disease as a bronchopneumonia, the roentgenologic features of which do not differ materially from bronchopneumonia due to other organisms. This stage of the disease is of such short duration that it is unlikely that many patients are examined by means of the roentgen ray during this period. Only one of our patients was examined this early in the disease (case 1).

The lobular patches of the primary bronchopneumonia coalesce rapidly to form larger areas which give the lung the appearance of lobar pneumonia. This differs from an ordinary pneumococcal lobar pneumonia in that the consolidation does not appear to be as complete and homogeneous and is not as definitely limited to a single lobe. The involvement is usually most intense in the periphery of the lung. Several such consolidations may be present in the same or the opposite lung. These characteristics have given rise to the condition being known as a pseudolobar pneumonia.

After a variable length of time, less rapidly in the nonfatal cases, extensive destruction of the tissue of the lung in the involved areas occurs, which lead to the formation of multiple abscesses and cavities. This gives rise to a characteristic roentgenographic appearance, which differs from all other acute pulmonary infections with the possible exception of influenza. A distinctive feature of these abscesses and cavities is their extremely thin walls to which attention was called by Belk and roentgenologically by Westermarck.

It is in this stage that the disease usually terminates fatally. In those exceptional cases in which recovery occurs we have learned from our roentgenologic studies that the involved areas of the lung become the seat of an extensive fibrosis often with the persistence of cavities. We believe this residual fibrosis to be more or less permanent.

On the basis of this pathologic condition, we recognize roentgenologically four distinct stages of the disease. The first is the stage of primary bronchopneumonia, the second, the stage of pseudolobar pneumonia, the third, the stage of formation of multiple abscesses and cavities and the fourth the stage of fibrosis.

## REPORT OF CASES

CASE 1—J. A., a slightly undernourished Italian, aged 50, was admitted to the service of Dr. Alfred Stengel in diabetic coma. The diabetes had been known to exist for three years, and during this time there had been lapses in the diabetic regimen, especially just before admission to the hospital. During the week before admission, he had spat up some dark red blood which he believed

came from the mouth. On admission, the blood sugar was 0.411 per hundred cubic centimeters and the plasma bicarbonate 13 per cent by volume. The chest was emphysematous in type but apparently was clear. The diagnosis was severe diabetic acidosis probably partially induced by some infection. The urine showed albumin varying from a trace to a cloud, and many casts of the hyaline, waxy, and light and dark granular variety. Four days after admission, the blood urea nitrogen was found to be 86 mg per hundred cubic centimeters and during the next few days rose to 105 mg. Large doses of insulin were necessary to control the sugar level. Eight days after admission, facial cyanosis was distinct, and the patient complained of pain in the right side of the chest. Numerous frictions were heard in the right anterior axillary line at the level of the fourth rib. Posteriorly over the right lower lobe the percussion note was impaired and the breath sounds suppressed. It was thought that the patient probably had a low grade bronchopneumonia. A roentgenogram of the chest (fig 1), taken the following day, was reported as suggesting a resolving pneumonia of the entire right lung.

For the following fourteen days, the general condition of the patient improved slightly. Fever continued, the temperature going as high as 100 F. The physical



Fig 1 (case 1)—Friedlander's pneumonia. The primary stage of bronchopneumonia.

signs in the chest came to involve a slightly greater area. X-ray examination at this time (fig 2) showed that the pneumonic process had condensed into areas assuming a pseudolobar appearance. By this time, Friedlander bacilli began to appear in the sputum in large numbers both on smear and on culture. At this time the temperature varied between 99 and 101. Blood culture was entirely negative. Pneumococci or acid-fast organisms were not found on repeated examinations. The Wassermann reaction of the blood was negative.

Thirty-two days after admission, the physical signs in the right side of the chest remained practically unchanged, but X-ray examination (fig 3) at this time showed multiple cavitation throughout the entire right lung. The sputum continued to show Friedlander's organisms in large numbers. During the next eight days the blood urea nitrogen had returned to normal, twenty-eight days having elapsed since it was 105 mg per hundred cubic centimeters. Also during this time the blood sugar level became more definitely stabilized, ranging between 170 and 220 mg per hundred cubic centimeters. From this time on there was no fever, although the improvement in the general condition of the patient was slight and extremely gradual. The physical and X-ray signs in the chest remained much the same except that the roentgenograms (fig 4) showed that the cavities in the right lung were draining well. Friedlander's organisms con-

tinued to appear in the sputum. The patient now steadily improved and the diabetic situation was controlled in a satisfactory manner. He was discharged from the hospital 102 days after admission.

After he left the hospital, his general condition was good. Six months later he was admitted to the University Hospital, again for diabetic acidosis. On this admission, as on the previous one, he gave the history of having spat up blood

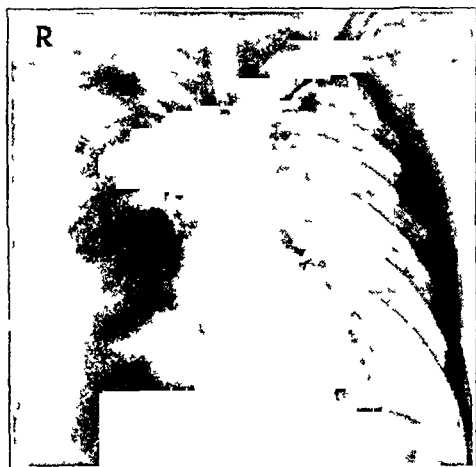


Figure 2



Figure 3

Fig. 2 (case 1) —The pseudolobar stage

Fig. 3 (case 1) —The stage of multiple abscess and cavity formation

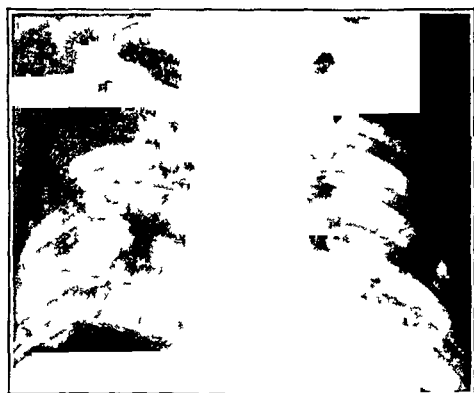


Figure 4



Figure 5

Fig. 4 (case 1) —The stage of fibrosis, showing the appearance of the lungs at the time of the patient's discharge from the hospital

Fig. 5 (case 1) —Chronic stage, approximately ten and one-half months after the onset of the acute pneumonia

a few days before admission. The diabetes was controlled more easily on this occasion. The striking aspect concerning the chest was that physical signs still remained over the right lung, and the roentgenograms (fig. 5) showed a diffuse scarring with lines marking the walls of the former abscess cavities.

CASE 2—M P, a thin white woman, aged 50 was admitted to the Hospital of the University of Pennsylvania, to the service of Dr Alfred Stengel, on Feb 9, 1927 Her chief complaint was cough and weakness For a year previous to admission, she had complained of general weakness and a slight cough productive of a moderate amount of yellowish expectoration However, her appetite had been good, she had not felt as if she had fever, and during the year she had lost only 3 pounds (1.4 Kg) In August and in December, 1926, she had had grip, convalescence from the latter attack being slow

On the morning of Jan 30, 1927, she was awakened by an attack of coughing accompanied by a small amount of sputum tinged with bright red blood The same thing occurred once on each of the two following days On Feb 4, 1927, she arose feeling weak and chilly, and was found to have a temperature of 102 F The weakness, fever, cough and expectoration continued until she was admitted to the hospital On February 6, she began to have pain, worse on deep breathing, in the lower portion of the left axilla, and this continued until she was admitted to the hospital



Figure 6



Figure 7

Fig 6 (case 2) —The pseudolobar stage Heart retracted to the left

Fig 7 (case 2) —Third stage Large abscess in left upper lobe

The past medical, the family and the social history did not have any bearing on the present illness

On admission to the hospital, the temperature was 102 F, the pulse rate, 120, and respirations, 32 The blood pressure was 140 systolic, 80, diastolic The cheeks were flushed, but she lay quietly in bed and did not seem to be in pain Examination of the chest revealed dullness to percussion in the left axilla with bronchovesicular breathing and many subcrepitant râles Anteriorly, at the level of the third rib on the left side the percussion note was skodac, and on auscultation the condition was the same as that in the left axilla The tentative diagnosis was a partial consolidation of the left upper and left lower lobes X-ray examination (fig 6) suggested lobar pneumonia in the left upper and lower lobes with a retraction of the heart to the left The leukocyte count was 12,700, with 84 per cent of polymorphonuclears Organisms of the Friedlander type were present in the sputum Tubercle bacilli were not found on repeated examination The blood Wassermann reaction and blood culture were negative

During the six days after admission, the temperature slowly returned to normal and the general condition of the patient steadily improved During this



Figure 8



Figure 9

Fig 8 (case 2) —Lateral view Same as figure 7

Fig 9 (case 2) —Appearance of the lungs at the time of discharge from the hospital It should be noted that the lesion in the left lower lobe had not changed and that the heart is still retracted to the left

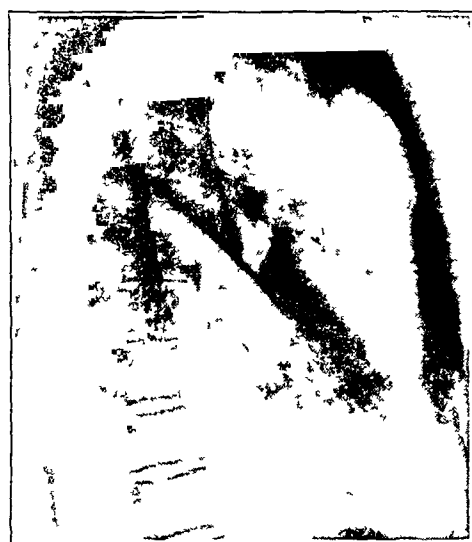


Figure 10



Figure 11

Fig 10 (case 2) —Lateral view, same as figure 9, which best shows the large cavity in the left upper lobe with marked thickening of the interlobar pleura

Fig 11 (case 2) —Appearance six and one-half months after date of discharge It should be noted how little change has occurred in that time

time the left lung showed a tendency to clear, but after ten days the physical signs failed to improve. Three weeks after admission x-ray examination showed a large consolidation limited to the lower portion of the left upper lobe, and one week later this area had broken down with the formation of a large cavity (figs 7 and 8). The roentgenograms of the chest showed that there was a fluid level in this cavity. The lesion in the left lower lobe had not changed. The temperature was normal, and the patient complained of nothing except moderate weakness. During this time, the Friedländer organism was recovered from the sputum repeatedly.

The patient steadily improved. An area of percussion dullness persisted at the left base, just to the left of the cardiac dullness, where there was some suppression of breath sounds and many subcrepitant râles. The temperature remained normal. Repeated x-ray examinations of the chest showed that the abscess in the left upper lobe apparently was draining well (figs 9 and 10). The patient was discharged from the hospital on April 6.

During the summer of 1927, her general condition was good. One morning in July, just after arising she coughed up about a fourth of a cup of bright red



Figure 12



Figure 13

Fig 12 (case 3) —Appearance of lungs on admission. Pseudolobar stage.

Fig 13 (case 3) —Appearance approximately six weeks after admission, showing third stage in the left upper lobe and fourth stage in the right upper lobe.

blood. She had not had respiratory symptoms before this and had not been engaging in any unusual physical exertion. Further hemoptysis had not occurred. When this paper was written, she felt well. Physical examination still revealed signs at the left base. X-ray examination (fig 11) showed a cavity still remaining in the region of the old abscess with fibrosis in the left base.

CASE 3—T. M., a well developed negro, aged 43, was admitted to the service of Dr. Alfred Stengel with the history and symptoms of acute lobar pneumonia. He had "caught cold" two weeks before admission, later developing pain in the right lower quadrant of the chest and yellowish sputum streaked with blood. During the past nine years, he had had five attacks of lobar pneumonia. In 1919 he had had a chancre for which he had been treated. The family and social history were irrelevant.

On admission to the hospital, the temperature was 103 F, the pulse rate, 124 and respirations, 40. The blood pressure was 70 systolic, 35, diastolic. Physical examination showed signs of consolidation over the right upper and the left lower lobes. The leukocyte count was 11,600. On culture the sputum showed

organisms of the Friedlander type and no pneumococci. Subsequently, Friedlander's organisms were isolated from the sputum repeatedly. Pneumococci or acid-fast bacilli were not found at any time. The blood Wassermann reaction and blood culture were negative.

During the first five days after admission the general condition of the patient improved, the temperature returned to normal by lysis, and the signs in the chest showed a tendency to improve. On the ninth day following admission, the patient became febrile and remained so for the following forty-five days. During a large part of this period, the temperature curve was septic in type. Chills and sweats were common. During this period, the patient became increasingly weaker. From the standpoint of physical examination, the outstanding symptom was the extreme indolence of the lesions in the lungs. The signs, at times, suggested a loculated or interlobar empyema. Repeated x-ray examinations of the chest tended to confirm this suspicion. Several attempts to locate fluid or pus with the exploratory needle failed. Finally, on the fifty-fourth day after admission, the temperature became normal and remained so. From this time on the patient made an uninterrupted recovery. At the time this paper was written, he was working in a brickyard and felt entirely well symptomatically.

The roentgenographic features of this case differed somewhat from those of the other two. On admission the appearance was that of consolidations involving the right upper and left lower lobes (fig 12). Two weeks later there was considerable improvement in the lesion in the right upper lobe and no change in the left lower lobe. Two weeks later a reinfection had occurred in the right upper lobe which was even more extensive than the original involvement. A slight improvement was noted in the left lower lobe. Three weeks later it was found that the lesion in the right upper lobe had been replaced by a marked fibrosis and that the lesion in the left lower lobe had almost entirely disappeared. In addition, however, there was now a marked involvement of the left upper lobe which was undergoing formation of multiple abscesses and cavities (fig 13). Ten days later the patient was discharged. A roentgenogram made at this time showed fibrosis of the right upper lobe with multiple abscesses in the left upper lobe. This case well illustrates the migratory nature of Friedlander's pneumonia.

#### COMMENT

We well realize the fact that the blood cultures were negative in these patients. However, to the best of our knowledge, all cases of Friedlander's pneumonia in which the organism has been recovered from the circulating blood have ended fatally. The repeated recovery of this organism in profuse growth from the sputum would point toward its being the etiologic agent. Our bacteriologic proof is not absolute but the other symptoms, clinical and roentgenographic, justify, we believe, the conclusion that the pulmonary lesions here described were produced by the Friedlander bacillus.

We believe, further, that the disease constitutes a distinct entity, one which can be and should be differentiated from other pulmonary infections. The acute form is most likely to be mistaken for bronchopneumonia or lobar pneumonia. Here one would have to rely on the clinical course, the bacteriologic and roentgenologic studies to make the

differentiation. Occasionally, one sees an influenzal pneumonia which may closely simulate Friedlander's pneumonia. The clinical course is often similar, and the disease may terminate with multiple cavitation and fibrosis. Aside from the absence of the Friedlander bacillus in such cases, we find roentgenologically that the principal involvement is in the tissues adjacent to the hilum, while in Friedlander's pneumonia the pathologic change is chiefly in the parenchyma of the lung.

Probably the most important aspect of Friedlander's pneumonia, particularly the chronic form, is its close resemblance to tuberculosis. So closely may these diseases simulate each other that in certain cases neither the clinical nor the roentgenologic evidence serves to make the differentiation. The diagnosis must rest on the bacteriologic examina-



Fig 14—Chronic Friedlander infection of the left lung

tion alone. This has led us to the belief that undoubtedly many cases of chronic Friedlander infection are masking under the diagnosis of tuberculosis. A case in point has recently come to our attention.

A white man, aged 61, was admitted to the University Hospital (service of Dr Alfred Stengel) because of symptoms in the stomach apparently due to pyloric carcinoma. He gave a history of cough and expectoration of long standing. The expectoration was a thick muco-purulent material. At the age of 41, or 20 years before admission, he had pneumonia. Since that time he had been told that he had "a bad left lung." Because of this, at one time he spent three months in a tuberculosis sanatorium, but the tubercle bacillus was never found in the sputum. Repeated examinations on this admission also gave negative results, but instead the Friedlander bacillus was recovered in large numbers. The x-ray examination (fig 14) revealed a lesion involving the entire left lung with retraction of the heart and mediastinal structures toward the affected side. There was marked thickening of the pleura, extensive fibrosis and numerous cavities throughout the lung.



We believe that this pathologic condition dates back to the pneumonia that he had twenty years before admission, and that this case presents sufficient evidence to warrant the diagnosis of a chronic Friedlander infection of the left lung

Case 2 of our series with the history of repeated attacks of grip, hemoptysis, cough and weakness might readily have led one to suspect tuberculosis. This case, we believe, was a chronic Friedlander infection with an acute exacerbation which caused the patient's admission in February, 1927. Our reasons for this conclusion are based on the history of the case plus the x-ray evidence of an old fibrosis of the left lower lobe causing a retraction of the heart to the left. The roentgenograms show that these symptoms were constant during the entire time the patient was under observation.

On the basis of our studies, we believe that Friedlander's pneumonia, particularly the chronic form, is far more common than is generally supposed. Its close resemblance to chronic pulmonary tuberculosis makes its recognition and differentiation important.

#### SUMMARY

1 Three cases of pneumonia due to the Friedlander bacillus are reported.

2 In two cases the onset suggested bronchopneumonia and in one lobar pneumonia.

3 The temperature fell by lysis in all cases, and in all the total leukocyte count tended to be lower than that seen in the usual case of lobar pneumonia.

4 The outstanding physical manifestation was the extreme indolence of the lesion of the chest.

5 There are characteristic x-ray symptoms which serve to differentiate this condition from other pulmonary infections.

6 Several months after the acute infection evidence of pathologic change can still be demonstrated both by physical and by x-ray examination.

7 From our studies we believe that there is a chronic form of pulmonary disease due to the Friedlander bacillus.

8 This chronic form is in many respects similar to chronic pulmonary tuberculosis. We therefore feel that in cases of suspected tuberculosis in which the organisms cannot be found the sputum should be examined for the Friedlander bacillus.

# THE CHOLESTEROL CONTENT OF BLOOD PLASMA IN DIABETES MELLITUS

A STATISTICAL STUDY BASED ON TWO THOUSAND OBSERVATIONS  
IN THREE HUNDRED AND EIGHTY-FIVE CASES \*

I M RABINOWITCH, M D

MONTREAL

Estimation of the cholesterol content of blood plasma is now part of the routine management of the diabetic patient in the Montreal General Hospital. Estimations are made at least on the admission of patients to the hospital and on their discharge and thereafter as regularly as possible, on their return to the clinic for the treatment for diabetes. All estimations are made on blood obtained from patients in the fasting state at least fifteen hours after the evening meal. Should patients require insulin, tests are made, as for blood sugar, not only before food is given, but before the administration of this drug. The present report is concerned with the study of 2,000 estimations made in 385 cases. All tests were made, not only under these standard conditions, but by the same technic and by the same laboratory workers. Patients observed for periods of less than six months are excluded from this study.

Plasma cholesterol is made use of as an index of lipid metabolism in cases of diabetes mellitus for the following reasons: 1 It is a relatively stable chemical compound. 2 Its estimation is relatively simple. With reasonable care, no difficulties are encountered.<sup>1</sup> By the method employed,<sup>2</sup> recovery of added cholesterol is quantitative within the accepted limits of experimental error. 3 Plasma cholesterol values tend to run approximately parallel to those of the total fatty acids. Therefore, any changes of the latter are reflected in the former.

Interest in this phase of diabetes mellitus was first stimulated by the publications from Joslin's clinic and those of Professor Bloor.<sup>3</sup> These

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\* From the Department of Metabolism, The Montreal General Hospital, Montreal

1 Before applying the Lieberman-Burchard reaction in this test, colorimetric difficulties are entirely overcome if the alcohol-ether extract is allowed to evaporate to dryness for a period of hours in a drying oven at a constant temperature, rather than for a short period of time on a stove, as originally recommended by Bloor. By the former procedure, the development of the brownish color frequently encountered when the stove is used and which interferes with color reading, does not take place. The resulting solution is clear, and colors are easily matched.

2 Bloor, W R. J Biol Chem 24 227, 1916

3 Joslin, E P, Bloor, W R, and Gray, H. The Blood Lipoids in Diabetes, J A M A 69 375 (Aug 4) 1917

authors, by correlating their laboratory data with the various clinical types of diabetes, showed that "all types of diabetes are distinguished by a marked increase in the lipoids of the blood, and the general statement can be made that the increase is progressive with the seriousness of the disease" A rather important observation was that parallelism did not exist between the fluctuations in the blood sugar and lipid, and that the amount of blood sugar present was not nearly as accurate a test of the severity of the disease as was the amount of blood lipoids In a more detailed study, one of the workers of this group<sup>4</sup> again demonstrated a relationship between the lipid content of the blood and prognosis "The longer the duration of the disease before examination the lower the blood fat, presumably because those patients live long who have low fats, that is, mild diabetics" In his recent monograph, Joslin<sup>5</sup> briefly summarized the present knowledge of the physiology of the blood lipoids and in a striking manner further illustrated the prognostic value of their determination

In a previous report of experiences with 254 subjects and a much lesser number of estimations than presently available, I<sup>6</sup> was able to confirm some of the observations made by Joslin and his co-workers It was shown that the cholesterol content of the blood is a better index of the course of diabetes than the blood sugar Patients may, on discharge from the hospital, have a normal amount of blood sugar and the urine may be free from sugar In many of these cases, the cholesterol content of the blood is increased By observing these patients as they return to the outdoor clinic, differences in progress are noted The course of the patient who has a normal amount of blood sugar but a high cholesterol content does not, on the average, appear to run as uneventful for the same length of time as that of the patient who has not only a normal amount of blood sugar, but also a normal amount of cholesterol When there is a large amount of cholesterol, the slightest dietary indiscretions result in more marked and more persistent hyperglycemia than when the cholesterol content is normal Hyperglycemia resulting from slight illnesses appears to be more frequent with a large than with a normal amount of cholesterol, and when the cholesterol is increased, the incidence of neuritis and of vascular changes is greater (Though neuritis, and even gangrene, may be observed in persons with a normal cholesterol content, the number of such cases is not sufficiently great to affect the rule) The relationship between a large amount of cholesterol in the blood and

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4 Gray, H. *Am J M Sc* **168** 35, 1924

5 Joslin, E. P. *Treatment of Diabetes*, ed 4, Philadelphia, Lea & Febiger, 1928

6 Rabinowitch, I. M. *J Canad M A* **17** 171, 1927

gangrene is striking Plasma cholesterol is also related to acidosis, though the relationship is not strictly quantitative

The response of plasma cholesterol to treatment, either by diet alone or with insulin, differs not only with the severity of the disease, but with the type of the diabetic patient The different types of curves obtained from data recorded at regular intervals appeared to be characteristic In my experience, as will presently be shown, it is one of the best methods of estimating not only prognosis, but progress

A few examples are cited

A patient known to require insulin is discharged from the hospital His urine is free from sugar and acetone bodies, the blood sugar is normal, and the plasma cholesterol is normal He returns some time later to the clinic with a history of not having followed his diet and also of frequent appearances of sugar in the urine The following are possible results in such cases (a) blood sugar increased, plasma cholesterol normal, (b) blood sugar increased, plasma cholesterol increased

In the former case, diet alone is usually sufficient to reduce the blood sugar to the normal level The blood sugar usually falls rapidly In spite of dietary indiscretions, carbohydrate tolerance apparently has not been impaired The urine can still be kept free from sugar and acetone bodies and the blood sugar normal on a diet compatible with normal requirements

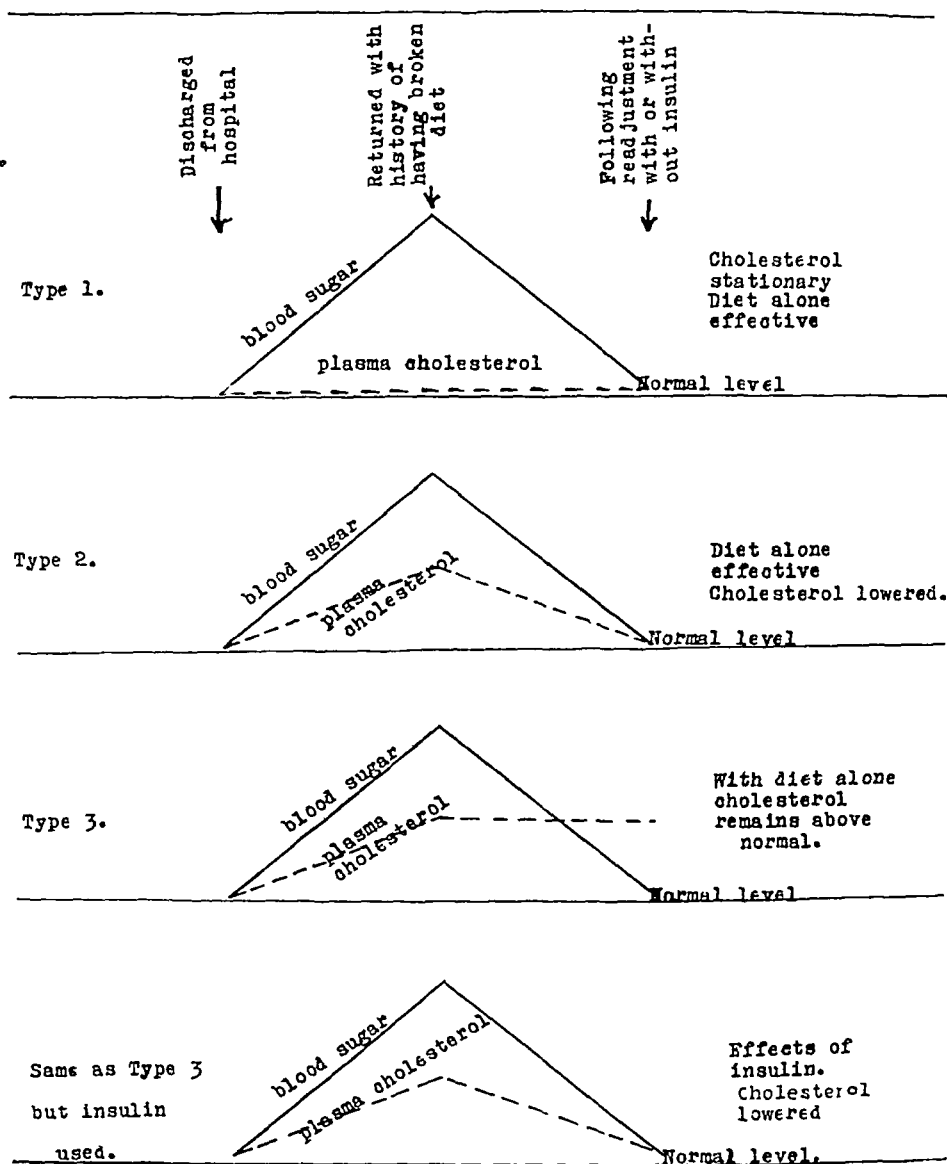
When, however, besides a hyperglycemia, hypercholesterolemia is also present, the blood sugar may not return to the normal level after restriction of diet alone, if it does, it does so much more slowly than when the cholesterol content is normal

The cholesterol itself may or may not return to the normal level after readjustment of diet Should it not return to the normal level, insulin is usually found necessary to maintain ideal conditions, namely, a normal blood sugar and urine free from sugar and acetone bodies when the patient's diet is compatible with the requirements The possible results are diagrammatically recorded in the accompanying chart

Since it is possible to decrease the cholesterol content of blood plasma, either by regulation of the diet alone or by such regulation plus insulin, the values found when patients are first seen, that is, prior to treatment, have limited significance in the estimation of progress Two extreme examples are cited in table 1 to demonstrate how rapidly reductions may take place following the use of insulin On admission to the hospital, both patients had severe acidosis

The following are examples of reductions of cholesterol following treatment of patients with a less severe form of diabetes, that is, patients with glycosuria and hyperglycemia, but without acetonuria One of these patients (W S F) did not require insulin, and the other patient (Case No 13818/26) did

Persons with diabetes, in whom the disease is complicated by infection, may, as is well known, fail to respond even to massive doses of insulin. The plasma cholesterol is particularly of value here. Since there is a relationship between lipemia and acidosis, data on cholesterol tend to indicate the degree of susceptibility of such patients to this



Diagrammatic representation of the relationship between plasma cholesterol and progress of patients who do not follow diets

complication. The following is an example. The patient (#1002127) was admitted to the hospital with diabetes complicated by pneumonia. At the time of admission, the urine contained a large amount of sugar, but no acetone bodies. During the febrile state, the reaction to insulin was practically nil. Marked glycosuria persisted. Acetonuria was not

present The plasma cholesterol was below the normal average, namely, 0.145 per cent The prognosis therefore appeared to be good The patient recovered Following the crisis, the urine became sugar-free and remained so without the use of insulin On discharge from the hospital, the patient was, and still is, on a diet consisting, approximately, of 150 Gm of carbohydrates

Carotinemia and cholesterolemia appear to be related This combination of conditions was previously reported <sup>7</sup> Interpretation of cholesterol

TABLE 1—*Rapid Reduction of Cholesterol Content in Two Cases of Severe Diabetes*

Case 5728/28		Case 5517/28	
Date	Cholesterol, per Cent	Date	Cholesterol, per Cent
Oct 7, 1928	1.380	Sept 28, 1928	0.925
Oct 8, 1928	0.980	Oct 1, 1928	0.595
Oct 9, 1928	0.640	Oct 11, 1928	0.406
Oct 10, 1928	0.520		

TABLE 2—*Reduction of Cholesterol in Less Severe Cases of Diabetes*

W S F		Case 13818/26	
Date	Cholesterol, per Cent	Date	Cholesterol, per Cent
Jan 7, 1927	0.400	Dec 14, 1926	0.401
Jan 28, 1927	0.292	April 12, 1927	0.222
March 8, 1927	0.223	May 21, 1927	0.229
July 15, 1927	0.212		

TABLE 3—*Cholesterol Data in a Case of Carotinemia and Cholesterolemia*

Case 6049/27	
Date	Cholesterol, per Cent
Nov 23, 1927	0.456
Nov 26, 1927	0.347
March 1, 1928	0.476
May 1, 1928	0.709
Aug 29, 1928	0.512

data in such cases is difficult Since vegetables are known to contain cholesterol-like bodies, limited significance must be attached to the observations in these cases, except that carotinemia, by itself, suggests unfavorable prognosis Table 3 shows the cholesterol data in such a case The patient died recently of a cerebral hemorrhage

It is remarkable that in spite of patients' persistent disregard of dietary regulations, and although they have persistent glycosuria, the plasma cholesterol may remain within the normal limits The prog-

nostic significance of cholesterol in these cases is suggested from the fact that such patients appear to make good progress in spite of the misleading laboratory data. Such cases, however, are few.

The reverse of this picture is shown in the type of case in which the amount of cholesterol increases in spite of the fact that the patient follows the prescribed diet rigidly. The number of these cases also is few. An example is shown in table 5.

TABLE 4—*Cholesterol Data in a Case in Which Diet Is Disregarded*

Case 3388/27	
Date	Cholesterol, per Cent
June 30, 1927	0.197
July 4, 1927	0.192
July 9, 1927	0.197
July 25, 1927	0.179
Aug. 5, 1927	0.188
Feb. 23, 1928	0.166
May 1, 1928	0.191

TABLE 5—*Cholesterol Data in a Case in Which Diet Is Followed*

Metabolism Laboratory 160	
Date	Cholesterol, per Cent
April 1, 1927	0.191
June 2, 1927	0.190
July 7, 1927	0.185
Sept. 30, 1927	0.192
March 24, 1928	0.277
May 5, 1928	0.350

TABLE 6—*Case in Which Synthalin Was Used*

Date	Plasma Cholesterol, per Cent	Remarks
April 19	0.219	Before treatment
April 22	0.180	Three days after treatment
May 13	0.204	
June 9	0.181	
July 9	0.158	
July 15		Insulin replaced by synthalin
July 25	0.222	
August 5	0.205	
September 19	0.245	
October 17	0.303	

Synthalin, unlike insulin, apparently fails to control cholesterolemia. This was shown in a previous report.<sup>8</sup> The patient requires insulin, but the diabetes has been kept under control with synthalin for the past fifteen months. The results in another case in which the patient requires insulin and has been receiving synthalin since August, 1927, are given in table 6.

<sup>8</sup> Rabinowitch, I. M. An Unusual Case of Diabetes and Gout, J. Canad. M. A. 21: 682, 1928.

It will be noted that the cholesterol values are distinctly higher and are increasing since the use of insulin was discontinued

An objection which may be raised to these observations is that the few cases cited may be exceptions rather than the rule, and that a study of average values of a large series of cases would be of greater value. Fortunately, the number of patients who have been observed and the cholesterol estimations which have been made are large and sufficient

TABLE 7—*Plasma Cholesterols and Their Incidences Based on Two Thousand Observations*

Plasma Cholesterol, per Cent	Incidence
175	334
176 - 200	246
201 - 225	272
226 - 250	296
251 - 275	224
276 - 300	218
301 - 325	104
326 - 350	106
351 - 375	50
376 - 400	34
401 - 500	76
500 +	40

TABLE 8—*Subjects Grouped According to Laboratory Data*

Group	Laboratory Data
1	Urine sugar-free, blood sugar normal
2	Urine sugar-free, blood sugar less than 0.18 per cent
3	Glycosuria once a month
4	Glycosuria twice a month
5	Glycosuria once a week
6	Glycosuria twice a week
7	Glycosuria daily, but free at times
8	Glycosuria persistent

TABLE 9—*Average Cholesterol Values for Subjects in Table 8*

Group	Cholesterol, per Cent
1	0.184
2	0.209
3	0.230
4	0.252
5	0.272
6	0.288
7	0.320
8	0.379

to enable statistical treatment of the data. The results of such treatment are given in table 7, they appear to demonstrate definitely the value of plasma cholesterol from the point of view of progress.

In table 7 are shown plasma cholesterols and their incidence in 2,000 instances.

In order to determine whether or not the cholesterol content of the blood plasma is related to the degree of control of the disease, all subjects were grouped according to the laboratory data, as shown in table 8.

The average cholesterol values were calculated for each group. The results are shown in table 9.



The question which arises is, Are the differences between the averages of the various groups significant? In order to attempt to answer this question, the following values were calculated for each of the groups mentioned (a) number of cases, (b) average percentage of cholesterol, (c) standard deviation and (d) probable error of the mean. These are recorded in table 10.

With this information, it is possible to determine whether the differences observed between the means of any two groups one wishes to

TABLE 10—*Showing Arithmetical Means, Standard Deviations and Probable Errors of the Means of Plasma Cholesterol Percentages Grouped According to the Degree of Control of Diabetes*

Group	Number of Observations (N)	Arithmetical Mean (A M)	Standard Deviation ( $\sigma$ )	Probable Error of Mean ( $0.67449 \frac{\sigma}{\sqrt{N}}$ )
1 Urine sugar free blood sugar normal	314	0.184	57.1	3.1
2 Urine sugar-free blood sugar less than 0.180 per cent	332	0.209	61.0	3.3
3 Glycosuria once a month	400	0.230	52.1	2.6
4 Glycosuria twice a month	260	0.252	59.8	3.5
5 Glycosuria once a week	246	0.272	63.6	3.8
6 Glycosuria twice a week	220	0.288	80.8	5.2
7 Glycosuria daily, but free at times	182	0.320	91.1	6.4
8 Glycosuria persistent	46	0.379	171.1	15.8

TABLE 11—*Showing Differences Between Means, the Probable Errors of the Differences and the Ratios of the Differences to the Probable Errors of the Differences*

Groups Compared	Difference Between Means	Probable Error of Difference*	Difference Probable Error of Difference
1 and 2	25	4.5	5.5
2 and 3	21	1.2	5.0
3 and 4	22	4.3	5.1
4 and 5	20	5.1	3.9
5 and 6	16	6.4	2.5
6 and 7	32	8.2	3.9
7 and 8	59	17.1	3.4

\* If  $p_1$  is the probable error of the mean of group 1, and  $p_2$  is the probable error of the mean of group 2, then  $\sqrt{(p_1)^2 + (p_2)^2}$  is the probable error of the difference.

compare are due to the control of the diabetes or the result of chance. Comparisons were made between the following groups: 1 and 2, 2 and 3, 3 and 4, 4 and 5, 5 and 6, 6 and 7 and 7 and 8. The necessary calculations were as follows: (a) the differences between the means, (b) the probable errors of the differences and (c) the ratios of the differences between the means to the probable errors of the differences. The results of these calculations are shown in table 11.

In each case, it is clearly demonstrated that the occurrence of the differences between the means of the groups compared were not the result of chance. The significance of the difference between the

average amounts of cholesterol of groups 5 and 6 is the only one in doubt. Even here, however, it may be shown that the odds against the occurrence of such a difference between the cholesterol content being the result of chance are about 10 to 1.

#### CONCLUSIONS

Plasma cholesterol affords a reliable index to the true progress of the diabetic patient.

Because of the simplicity with which the test can be carried out, estimation of the plasma cholesterol should form part of the routine management in diabetes.

As with all laboratory tests, in the interpretation of results obtained consideration should be given to other conditions which might lead to high values. These include jaundice, cholecystitis, pregnancy, nephrosis, etc.

# THE CHOLESTEROL CONTENT OF BLOOD PLASMA IN JUVENILE DIABETES

A STATISTICAL STUDY \*

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In a previous report<sup>1</sup> I demonstrated the value of cholesterol studies in diabetes from the point of view of progress. The demonstration, with the exception of a few cases cited as examples, was statistical. The data concerned adults only, since, as is well known, the diabetes of juveniles differs in many respects from that of adults. The report was based on 2,000 observations in 385 cases.

This brief report is concerned with the study of the cholesterol content of blood plasma in cases of juvenile diabetes. The various reasons for making use of plasma cholesterol as an index of lipid metabolism in diabetes were discussed in the first paper and, for purposes of brevity, are omitted here.

The literature on this phase of juvenile diabetes is scanty. There are various reasons for this. In the first place, the material available in any one clinic is relatively small, since juveniles represent only about 5 per cent of the total number of all diabetic patients. Another reason is that, judging from literature, lipid metabolism studies do not, except in a few clinics, form part of the routine management of diabetes. Joslin recorded his experience with twenty-six children. In one group of twenty-one cases the maximum, minimum and average cholesterol values were 0.109, 0.226 and 0.146 per cent, respectively, and in five cases of another group the corresponding values were 0.312, 0.500 and 0.385 per cent. Because of the limited material available at the time, Joslin hesitated to venture to interpret these values. It is obvious, therefore, that with the accumulation of more data, more will be known of this phase of diabetes, and it is for this reason that I wish to add to the literature my experience with this phase of the disease.

Forty-six children were studied<sup>1</sup>. This investigation was made along the same lines as that concerning diabetes in adults previously reported, that is, an attempt was made to determine, statistically, whether in juvenile diabetes plasma cholesterol is related to, and can afford an index of, progress. In order to determine the latter, the following studies were made: (a) a comparison between plasma chole-

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<sup>1</sup> From the Department of Metabolism, The Montreal General Hospital, and the Henry J. Elliott Laboratory of the Shriners' Hospital, Montreal

<sup>1</sup> Rabinowitch, I. M. The Cholesterol Content of Blood Plasma in Diabetes, Arch. Int. Med., to be published

terol of diabetic and nondiabetic children, (b) the relationship between cholesterol content of blood plasma and degree of control of diabetes, and (c) the relationship between cholesterol content of blood plasma and insulin dosage

Estimations were made on specimens of blood of forty-four normal children<sup>2</sup> under the same standard condition as previously described. Their ages ranged from 3½ to 14 years. Both sexes were fairly equally represented. There were twenty-three boys and twenty-one girls. Table 1 gives a brief summary of all of the analyses of the blood of both diabetic and nondiabetic patients.

TABLE 1—*Blood Analyses of Diabetic and Nondiabetic Patients*

Subjects	Cholesterol, per Cent		
	Maximum	Minimum	Average
Nondiabetic	0.234	0.111	0.176
Diabetic	0.600	0.120	0.243

TABLE 2—*Subjects Grouped According to Laboratory Data*

Group	Laboratory Data
1	Urine sugar-free, blood sugar normal
2	Urine sugar-free, blood sugar less than 0.18 per cent
3	Glycosuria once a month
4	Glycosuria twice a month
5	Glycosuria once a week
6	Glycosuria twice a week
7	Glycosuria daily, but free at times
8	Glycosuria persistent

As in the case of the adults studied in the attempt to determine whether there was any relationship between plasma cholesterol and the control of the diabetics, the subjects were grouped according to the laboratory data as in table 2.

Though this classification may appear arbitrary, it has, in my experience, been found practical. The average plasma cholesterol values were then calculated for each group. The results are shown in table 3.

TABLE 3—*Cholesterol Values for Groups in Table 2*

Group	Number of Cases	Average Plasma Cholesterol, per Cent
1	10	0.176
2	8	0.224
3	5	0.220
4	6	0.286
5	1	0.260
6	3	0.264
7	6	0.236
8	7	0.350

<sup>2</sup> This material was made available at the Shriners' Hospital for Crippled Children of Montreal. All of these children were normal with the exception of having congenital, or acquired, bone deformities (clubfeet, etc.)

It is obvious that, because of the small number of patients in each group, limited significance must be attached to the average values found. In order, therefore, to treat the data statistically, the numbers were increased by dividing all subjects into two groups, namely (a) those who had glycosuria and (b) those whose urines were sugar free.

Twenty belonged to the former and twenty-six to the latter group. The following values of each group were then determined: (a) arithmetical mean (average cholesterol), (b) standard deviation, (c) probable error of the mean. From these values were then calculated

TABLE 4—*Statistical Demonstration of the Relationship Between Control of Blood and Urine Sugar and Plasma Cholesterol*

Group	Number of Cases (N)	Average Cholesterol (M) per Cent	Standard Deviation ( $\sigma$ )	Probable Error of Mean†	Difference Between Means	
					Probable Error of Difference Between Means*	Probable Error of Difference
1. No glycosuria	20	0.184	37.4	5.6	14.8	6.9
2. Glycosuria	26	0.235	103.9	13.7		

$$\dagger 0.67449 \frac{\sigma}{\sqrt{N}}$$

$$* \sqrt{(5.6)^2 + (13.7)^2}$$

(a) the difference between the means and (b) the ratio of the difference between the means to the probable error of the difference. The results of these calculations are shown in table 4. It will be seen that the ratio of difference between the means to the probable error of the difference was 6.9. The latter figure makes it practically certain that the difference between the average amount of cholesterol of the two groups is the result of the degree of control of the diabetes and not the result of chance. In other words, children with glycosuria, that is, those in whom the diabetes is not controlled, tend to have a high cholesterol content of the blood.

Further proof of this conclusion was sought from another point of view. An attempt was made to determine whether there was any relationship between plasma cholesterol and insulin dosage. For this purpose all children were divided into four groups: (a) those for whom it has been necessary to increase the dosages of insulin, (b) those for whom the amounts required when first seen have remained unchanged, (c) those who were able to take decreased amounts, and (d) those who were able to discontinue its use entirely.

Table 5 shows the average values of plasma cholesterol of the different groups.

Again, the number of cases corresponding to each group was small, and in order to treat the data statistically, the children were divided

into two large groups, namely (a) those who were able to take a decreased dosage of insulin, and (b) those who were not able to do so. In each case, the same calculations were made. The results are recorded in table 6.

It will be seen that the ratio of the difference between the means to the probable error of the difference was 4.7. The odds against the occurrence of such a difference as found between the means, being the result of chance, were, therefore, about 650 to 1. In other words, it is certain that insulin dosage was related to the plasma cholesterol.

From the results obtained in these studies, it appears that the plasma cholesterol of juvenile diabetic patients affords the same index of

TABLE 5—Average Plasma Cholesterol Values

Group	Number of Cases	Average Plasma Cholesterol, per Cent
1	19	0.290
2	7	0.224
3	13	0.226
4	7	0.185

TABLE 6—Statistical Demonstration of the Relationship Between Insulin Dosage and Plasma Cholesterol

Group	Number of Cases (N)	Average Cholesterol (M) per Cent	Standard Deviation ( $\sigma$ )	Probable Error of Mean†	Probable Error of Difference Between Means*	Difference Between Means Probable Error of Difference
1 Able to decrease insulin	20	0.200	47.5	7.1	16.2	4.7
2 Unable to decrease insulin	26	0.277	110.5	14.6		

$$\dagger 0.67449 \frac{\sigma}{\sqrt{N}}$$

$$* \sqrt{(7.1)^2 + (14.6)^2}$$

progress for the child as it does for adults. In view, however, of the small number of observations, these results are reported not because I am convinced that they would apply to a larger series of persons, but in order that others, with similarly available data, may test the conclusion. As has been stated, in view of the low incidence of juvenile diabetes, the material available in any one clinic is small.

It is of interest here to note that in a study of the blood fat of diabetic children, Gladys Boyd<sup>3</sup> reached a somewhat similar conclusion, namely "Increasing tolerance indicating a more or less constantly normal blood sugar usually results in maintenance of the blood fat at the normal level."

3 Boyd, G. L. Blood Fat in Diabetic Children, *Am J Dis Child* **36**: 298 (Aug.) 1928.

# DIABETES MELLITUS

A STUDY OF ONE HUNDRED AND FORTY-SEVEN AUTOPSIES \*

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The present study is composed of an investigation of about 170 cases of diabetes mellitus in which autopsy had been performed. It was hoped that some correlation might be made of the clinical and pathologic observations. For this purpose we studied the clinical record, the protocol of the autopsy and the microscopic sections. From Dr von Glahn of the Presbyterian Hospital we obtained forty-nine cases, from Dr Rich of the Johns Hopkins Hospital thirty-six cases, from Dr Symmers of Bellevue Hospital twenty-five cases, from Dr Gross of Mount Sinai Hospital seventeen cases, from Dr Rohdenburg of the Lenox Hill Hospital eight cases, from Dr Denton of the New York Hospital eight cases and from Dr MacNeal of the Post-Graduate Hospital four cases. These cases date from 1909 to 1926, inclusively, and are therefore not duplicates of the series reported by Cecil.<sup>1</sup> In only 147 of the 170 cases reviewed did we obtain sufficient data for our purpose.

## CLINICAL DATA

*Age Incidence, Sex, Color and Nativity*—The ages ranged from 12 to 76 years. The distribution as to decades is given in table 1. Seventy-two of the patients were females and seventy-five males. There were 132 Caucasians, fourteen negroes and one Chinese. The native born patients numbered ninety-one, the Jewish, fifteen, the others were divided in groups of one to three between the countries of Europe.

*Family History*—Five cases presented a distinct history of diabetes in one or more members of the immediate family.

*Duration of Symptoms*—Twenty-two patients had had symptoms of diabetes for more than five years, thirty-six for more than one year, twenty-nine for more than six months, eighteen for less than six months, while nine had not had symptoms and the condition was discovered by the usual routine tests of the hospital. For the remaining eighteen cases there appeared no information in the history to indicate that the patient had been questioned as to the length of his illness. One

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~ From the Department of Pathology of Cornell University Medical College.

1 Cecil, R. L. Pathological Anatomy of the Pancreas in Ninety Cases of Diabetes Mellitus, J. Exper. Med. 11: 266, 1909.

patient had been under observation for twenty-five years because of diabetes

*Insulin*—Since the majority of patients died before the general use of insulin, we have not considered this factor in our statistics

#### GROSS AND MICROSCOPIC EXAMINATIONS OF PANCREAS

The description of the appearance and weight of the pancreas was neglected in many cases, and even when the weight is given one suspects the inclusion of extraneous fat and blood vessels. We have not tabulated these figures for this reason.

In every case the usual sections were stained with hematoxylin-eosin, and in almost all cases more than two portions of the organ were sectioned.

TABLE 1—*Age Distribution According to Decades in Patients with Diabetes*

Age	Cases	Interstitial Pancreatitis		Lipomatosis		Arteriosclerosis	
		Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
10 to 20	12	1	8	0	0	1	8
21 to 30	15	4	26.6	0	0	1	6.5
31 to 40	16	7	44	1	6.3	2	12.5
41 to 50	36	23	64	8	22	12	33.3
51 to 60	45	29	64	20	44.4	29	64
61 to 80	23	15	65	12	52	18	78

#### ASSOCIATED LESIONS OF OTHER ORGANS

*Endocrine Disorders*—Nine patients had adenomatous thyroids and one, colloid goiter. One showed hypoplasia of the suprarenals, another showed hyperplasia, while a third had fatty infiltration of the suprarenal cortex. Three cases were classed as status lymphaticus.

*Lesions of the Liver*—Of seven of the fifteen patients having cirrhosis of the liver, the condition was associated with hemochromatosis and one had a hepatic lobatum. All but two of these showed interstitial pancreatitis. Adams<sup>2</sup> referred to the frequent association of these two conditions. Sixty-seven showed some fatty change, and of these forty had definite fatty infiltration.

*Lesions of the Heart*—Root and Warren<sup>3</sup> were particularly impressed by the early occurrence of myocardial damage in diabetic patients. In their series of twenty-six patients, there were five under the age of 40 who showed coronary sclerosis, chronic myocarditis or coronary thrombosis. Sclerosis of the coronary vessels occurred in

<sup>2</sup> Adams and McCrae. A Textbook of Pathology, Philadelphia: Lea & Febiger, 1912, p. 595.

<sup>3</sup> Root, H. F., and Warren, S. Clinical Pathology of Twenty-Six Cases of Diabetes, Boston: M. & S. J. 45: 194, 1926.



twenty of our patients, but only one of them was under 40. Infarction of the ventricular muscle occurred in eleven patients, all of them over 40 years of age, while chronic myocarditis was present in nineteen over 40 and in one under 40. No relation was found between the degree of myocardial damage and that of the islands of Langerhans. In the group showing hemochromatosis, 43 per cent were affected with chronic myocarditis, but the factors producing the change here were obviously other than diabetic.

*Acute Infections*—Thirty-seven patients had suppurative lesions. Twelve had multiple abscesses, twelve cellulitis, eight perinephritic abscesses, two carbuncle and three otitis media. A surprising number showed ascending infections of the urinary tract, these numbered twenty-one, or 14.5 per cent. Thirty-six cases gave evidence of pneumonic involvement at autopsy.

#### LESIONS OF THE PANCREAS

*Interstitial Pancreatitis*—Interstitial pancreatitis was present in 123 cases, of which ninety-five or 64.8 per cent, showed interacinar, and twenty-eight or 19 per cent, interlobular, fibrosis. Cecil<sup>1</sup> found that 71 per cent of his cases showed interacinar, and 4.4 per cent, interlobular, fibrosis. If one disregards those cases in which only a slight increase in fibrous tissue occurred, there remain seventy-nine, or 53.7 per cent, of all our cases which showed a well developed interstitial pancreatitis. Table 1 gives the age incidence in interstitial pancreatitis and shows that, while this lesion is seen to increase with age, the high proportion of persons affected in middle life must be explained by some other factor. One that suggests itself is acute inflammation of the parenchyma, which heals by fibrosis. Six cases in the series bear out this theory.

CASE 121—The patient, aged 44, showed a pancreas which was the seat of a single large abscess surrounded by a thick fibrous wall. This had apparently been due to a perforated peptic ulcer. The onset of the diabetes occurred seven weeks prior to death.

CASE 47—A man, aged 54, was found to have an elongated abscess under the peritoneum in contact with the pancreas. He had been admitted to the hospital for cirrhosis of the liver with ascites, and gave no history of diabetic symptoms.

CASE 36—A man, aged 26, showed hemorrhage into the substance of the pancreas with leukocytes infiltrating the connective tissue. He gave a history of four weeks' duration of diabetic symptoms.

CASE 51—A man, aged 23, showed necrosis of the head of the pancreas with healing productive fibrosis. His symptoms had lasted two years.

CASE 90—A man, aged 75, showed hemorrhage into the fat and septums of the pancreas, with polymorphonuclear leukocytes in the extravasated blood. His symptoms had increased markedly in the six weeks prior to his death.

CASE 116—A man aged 62, showed marked edema of the fibrous tissue of the pancreas, which was invaded by wandering cells. He had been admitted for an infected hand and had not had symptoms of diabetes until admission.

These cases suggest that a possible etiology of the chronic productive fibrosis seen at autopsy may be the result of acute infections, and, further, that these acute inflammations may account for the sudden onset in certain cases of diabetes

Another cause of interstitial pancreatitis may be sought in its relation to gall bladder disease. Eleven patients of the series had chronic cholecystitis, and all but one had definite fibrosis of the pancreas. In ten cases stones were found in the gallbladder without evidence of cholecystitis, of these, six showed interstitial pancreatitis. In case 14a, the pancreas was represented by a long strand of fibrous tissue in which were embedded fairly numerous islands. It seems probable that at one time there had been an occlusion of the duct, and since a pancreatic

TABLE 2—*Effect of Interstitial Fibrosis on Island Cells*<sup>1</sup>

Island Lesion	Total Cases	Interstitial Pancreatitis		Capsular Thickening	
		Cases	Per Cent	Cases	Per Cent
Normal islands	11	3	28	3	27
Pyknotic islands	15	7	46	3	20
Slight fibrosis	31	11	45	17	55
Moderate fibrosis	23	11	48	16	70
Marked fibrosis	25	16	64	16	64
Hyaline islands	30	22	73	16	53
Hemochromatosis	7	7	100	4	57

\* Classification of Lesions of Islands of Langerhans

- I Normal islands
- II Fibrosis of islands
  - (a) Slight fibrosis
  - (b) Moderate fibrosis
  - (c) Marked fibrosis
- III Hyaline degeneration
- IV Pyknotic changes
- V Hemochromatosis
- VI Capsular thickening
- VII Hemorrhage into the islands
- VIII Giant nuclei

calculus was not found at autopsy, it may well have been caused by a stone in the ampulla. The organ resembled those described by MacCallum<sup>4</sup> after experimental ligation of the duct.

The effect of interstitial fibrosis on the island cells is definitely shown in table 2, that is, the more serious the damage to the islet, the greater is the percentage of interstitial change. Severe interacinar fibrosis results in atrophy of the parenchymatous tissue. This may account for the clinical observations of Jones, Castle, Mulholland and Bailey<sup>5</sup> who reported a series of diabetic cases, half of these showed diminished activity of the pancreatic secretions.

*Lipomatosis*—It seems possible that the atrophied tissue of the pancreas is replaced by fat. Lipomatosis of the pancreas is practically

<sup>4</sup> MacCallum, W. G. Relation of the Islands of Langerhans to Glycosuria, Bull. Johns Hopkins Hosp. **20** 265, 1909.

<sup>5</sup> Jones, C. M., Castle, W. B., Mulholland, H. B., and Bailey, F. Pancreatic and Hepatic Activity in Diabetes Mellitus, Arch. Int. Med. **35** 315 (March) 1925.

absent among patients under 40 years of age. Half of the patients over 60 are affected (table 1). Its incidence follows that of interstitial pancreatitis by about twenty years. In extreme cases the islands are isolated from the acini by areolar tissue.

*Tuberculosis*—Tuberculous lesions of the pancreas were not found in any case.

#### LESIONS OF THE ISLANDS OF LANGERHANS

Since serial sections were not available, figures of the number or size of the islands found in any case are not given. Adenomas of the insular tissue were not seen. While certain of the islands seemed larger than others, we are not able to present any observations that would substantiate the theories of regeneration and hypertrophy.

*Capsular Thickening*—Capsular thickening was present in 53 per cent of all cases. According to Otani,<sup>6</sup> there is no capsule for the normal island beyond the basement membrane of the surrounding acini. He regarded the capsule as a definite indication of interstitial inflammation. Other observers stated that the normal island is surrounded by a delicate connective tissue framework, one or more cells of which can be seen on section and which sends delicate strands into the island, these act as a support for the islet cells and carry the blood vessels and nerves. Capsular thickening occurred in conjunction with interstitial pancreatitis in 61 per cent of the cases. It appears to be more closely related to fibrosis of the islands, since in the normal and pyknotic group it was present in less than 30 per cent of the cases, while in the fibrotic groups it ranged from 55 to 70 per cent (table 2).

*Normal Islands*—In eleven cases changes were not noted in the cells of the islands. It is possible that there may have been damaged islands in uncut portions of the pancreas.

*Fibrotic Islands*—The most constant change noted was an increase in the connective tissue within the islands. This lesion has been referred to a "sclerosis" in other papers on this subject. The degree of fibrosis varied greatly in different islands of the same pancreas, and in scarcely any pancreas was there an absence of normal islands. In this the organ resembles the kidney, in which damaged and unchanged glomeruli lie side by side. We roughly classified the degree of fibrosis as (a) slight, (b) moderate or (c) marked, according to the extent to which the majority of islands were involved. The arrangement of the fibrous elements of a sclerosing island is like that of a tree, the trunk of which carries the blood vessel to the center of the island. Even though the fibrotic process is far advanced, the epithelial cells often

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<sup>6</sup> Otani, S. Studies on the Islands of Langerhans in the Human Pancreas, *Am J Path* **111** 1, 1927.

show remarkably good preservation. It is hard to believe, however, that the blood supply and the nerves are unimpaired.

*Hyaline Degeneration*—All grades of hyaline change are seen, from small amounts of extracellular, pinkish-staining, homogeneous material to complete replacement of an island. In these cases, it closely resembled a hyaline glomerulus. Advanced fibrosis is always present with this lesion and must be the precursor of it. A late, though not a common, process is calcification of these hyaline areas. Mallory<sup>7</sup> mentioned this condition in his textbook. We had one example of this in case 86, in a woman, aged 66, who had had symptoms for four years. The pancreas showed marked fat invasion, marked interstitial fibrosis of the acinar portions and extreme thickening of the arteries with calcified media. The islands varied from partial to complete hyalinization, and many were stained blue, the same color as the media of the artery.

*Hemochromatosis*—Seven of the patients had diabetes which was secondary to hemochromatosis. Two of the patients appeared not to have recognizable islands. Five showed definite fibrosis, but no hyaline change. The island cells had varying amounts of pigment, but were not otherwise different from the usual appearance of a normal cell.

*Pyknotic Changes*—In a limited number of cases, the islands stood out very clearly from the acinar tissue, owing to the fact that the nuclei were more deeply stained. On close examination the cells were seen to have small, darkly-stained nuclei, the chromatin network of which was nevertheless distinct. The cytoplasm was strongly acidophil. Of this group, only two showed evidence of insular fibrosis and in three giant nuclei were found. The other cases of this group did not show any change except in the pyknotic islands. That this is not a post-mortem change is clearly shown by the fact that there was no autolysis of the parenchyma as a whole in the region of the islands and that the pyknotic islands were seen in cases in which autopsy was performed early, that is, in case 104, one and a quarter hours post mortem and in cases 107 and 108, two hours post mortem. The average age of this group is the youngest of any in our series. Of the fifteen patients, one half died before the age of 40. Four died in their second decade, two in their third and two in their fourth.

*Hemorrhage*—In four cases, hemorrhage into the islands occurred. This was confined to the islands and did not appear in the surrounding parenchyma. One also showed slight fibrosis and another marked fibrosis of the islands. A third presented pyknotic islands and giant nuclei. The causes of death in the patients were lobal pneumonia, diabetic coma, cardiac failure and suppurative nephritis.

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<sup>7</sup> Mallory, T. B. Principles of Pathological Histology, Philadelphia, W. B. Saunders Company, 1918, p. 521.

*Giant Nuclei*—Slight variation in the size of the nuclei is expected, and this is one of the differentiating points between the alpha and beta island cells. Occasionally one sees an island with one or two nuclei about four times the diameter of its fellows. These do not differ in any respect from the other cells except in size. One of these five cases did not show other changes in the islands. The other cases were associated with pyknotic islands, and in one of them hemorrhage was present in an island.

#### CLINICAL SYMPTOMS

It soon became apparent to us that there were difficulties in estimating the severity of the diabetes in any given case on the evidence at hand in the clinical records. Estimations of blood sugar were made under varying conditions, patients were admitted and died from the effects of acute infections or from postoperative shock, in short, there was no criterion by which one could say with any scientific accuracy that a patient had mild or severe diabetes. We present the comments below for what they are worth.

*Coma*—There were fourteen cases of true diabetic coma uncomplicated by nephritis or infection. The following figures show the distribution according to damage of the islands: normal islands, one, pyknotic islands, one, slight fibrosis, three, moderate fibrosis, three, marked fibrosis, three, and hyaline islands, three. From this, it would appear that the degree of damage to the islands has little to do with the onset of coma. Of course, the series is small.

*Gangrene*—Twenty-three patients between the ages of 45 and 62 had gangrene of the extremities. Of those who lived beyond the age of 40, more than one in five developed gangrene. Seventy-five cases of the patients with gangrene had marked generalized arteriosclerosis and thirteen per cent had only moderate arteriosclerotic changes. The following figures give the relation of gangrene to damage of the islands: normal islands, in four cases, or 36 per cent of the group, pyknotic islands, three, or 20 per cent, slight fibrosis, seven, or 23 per cent, moderate fibrosis, two, or 9 per cent, marked fibrosis, five, or 20 per cent, and hyaline islands, two, or 7 per cent. Here, again, there does not appear to be any relation between the degree of change in the islands and the incidence of gangrene. It is highest in those showing the least damage and lowest in the hyaline group.

#### ANALYSIS OF SYMPTOMS IN CASES SHOWING ONLY NORMAL ISLANDS

Three patients had symptoms of less than six months' duration. Five had symptoms for from two to twelve years before death. In three cases, there was no record as to the duration or the symptoms. Six of the eleven patients were sugarfree on a diet without insulin.

Three died before a special diet was instituted, that is, within a few hours after admission. These data are suggestive, but again the series is too small to draw conclusions.

#### SUMMARY

1 A study of 147 cases of diabetes mellitus in which autopsy was performed was made with particular reference to the pathologic structure of the pancreas and the clinical course of the disease.

2 Interstitial pancreatitis was found in 123 cases, seventy-nine of which showed well advanced lesions. While this condition is more frequently present in older persons, it is often found in middle-aged persons. An explanation for this is offered in six cases showing acute inflammation of the interstitial tissue of the pancreas. A direct relation was found between the incidence of interstitial pancreatitis and lesions of the insular tissue (table 2). Tuberculous lesions in the pancreas were not found in any case.

3 Lipomatosis of the pancreas is a late result of atrophy of the acinar tissue due to interstitial pancreatitis.

4 Definite lesions of the islands of Langerhans were found in all but eleven of the cases studied. These lesions varied from difference in the staining reactions of the cells to fibrosis of the islands and hyaline degeneration. One case of calcified islands was seen.

5 No relation was found between the type of cases in which gangrene was present and the degree of damage to the islands. The same is true of coma.

6 An analysis of eleven cases without apparent damage to the islands showed that six patients did not have glycosuria when placed on a diet without insulin.

7 It is hoped that a simple test may be devised to enable one to correlate the severity of the diabetic condition. Until this has been done, it seems impossible to relate the clinical and pathologic observations in diabetes mellitus.

# THE EFFECT OF SYNTHALIN ON THE RESPIRATORY QUOTIENT OF THE DIABETIC PATIENT \*

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In 1926, Frank, Nothmann and Wagner <sup>1</sup> isolated a guanidine derivative, a diguanidyl decamethylene, which they called "Synthalin" This was reported to be effective in reducing blood sugar when taken by mouth and was suggested as a substitute for insulin in the treatment of diabetes Numerous publications have appeared, especially in Europe, concerning its use in diabetes and the possible mechanism of its action A supply of synthalin <sup>2</sup> was obtained for therapeutic trial on diabetic patients During the course of this investigation, a study was made of the respiratory quotients after a meal of dextrose It is believed that any drug reputed to have an insulin-like action must manifest itself by an increased oxidation of carbohydrate in the diabetic organism Blatherwick, Sahyun and Hill <sup>3</sup> stated that synthalin may possibly produce a hypoglycemia by an insulin-like action or by interfering with normal glyconeogenesis because of injury to the liver The present work supports the idea that synthalin does have an insulin-like action in that it aids in the utilization of carbohydrate in the diabetic organism Because of its toxicity, we believe that its clinical use is contraindicated The data in this paper are presented only as evidence concerning the possible mechanism of the influence of this guanidine derivative on carbohydrate metabolism

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\* From the Biochemical Laboratories of the Graduate School of Medicine of the University of Pennsylvania, and the Department of Metabolic Diseases, Philadelphia General Hospital

1 Frank, E , Nothmann, M , and Wagner, A Klin Wchnschr **5** 2100, 1926

2 Synthalin was supplied through the courtesy of Eli Lilly & Company, Indianapolis

3 Blatherwick, N R , Sahyun, M , and Hill, E J Biol Chem **75** 671, 1927

## EXPERIMENTAL DATA

Patients were selected at random, some with mild, others with severe cases of diabetes. They were kept in bed in the morning without breakfast, a blood sugar determination was taken while fasting, a specimen of urine obtained and the expired air collected in a Tissot spirometer for a period of ten minutes. The expired air was analyzed for carbon dioxide, oxygen and nitrogen with a Henderson-Haldane gas analysis apparatus. As the collection of urine from patients over short periods was unreliable, we assumed that 15 per cent of the total calories came from protein rather than attempt to calculate the protein metabolism from the nitrogen in the urine. After the total calories from the oxygen consumption were obtained, the calories produced by the oxidation of carbohydrate were determined by the triangular map of DuBois.<sup>4</sup> The grams of carbohydrate utilized were calculated by dividing the carbohydrate calories by 4.1. Approximately one hour after the blood sugar during fasting was taken a meal of dextrose was given, generally 0.5 Gm. of dextrose per kilogram of body weight, in one patient with a mild case of diabetes, however, 1.5 Gm. was administered. The blood sugar was then measured at intervals of one-half, one, two and three hours. Specimens of urine were collected for three hourly periods. Collections of expired air were made at approximately three-quarter hour intervals for the three-hour period. Special attention was paid to the attainment of normal respiration in all patients, as over or under ventilation causes appreciable error in the respiratory quotient. For the periods in which the patient received synthalin, these experiments were duplicated as closely as possible, with the exception that synthalin was given one or more hours previous to the meal of dextrose. As a preparation for both the control periods and the periods during which synthalin was given, the administration of insulin was discontinued at a similar time, previous to both experiments and for a sufficient interval to obviate appreciable effects of the insulin on the utilization of carbohydrate. The determinations for blood sugar were made by the method of Folin and Wu,<sup>5</sup> and the presence of sugar in the urine was determined by the method of Sumner.<sup>6</sup> A similar study of the respiratory quotient has been used by Petty and Stoner<sup>7</sup> to differentiate diabetes from benign glycosurias. Repeated studies have confirmed the observation that the respiratory quotient of patients with true cases of diabetes will not rise

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4 DuBois, E. F. *J. Biol. Chem.* **59** 43, 1924

5 Folin, O., and Wu, H. *J. Biol. Chem.* **41** 367, 1920

6 Sumner, J. B. *J. Biol. Chem.* **62** 287, 1924

7 Petty, O. H., and Stoner, W. H. *Am. J. M. Sc.* **171** 842, 1926



appreciably after a meal of dextrose, while patients with so-called renal diabetes give a normal response, with the respiratory quotient approaching 1

# REPORT OF CASES

CASE 1—J W, a man, aged 62, who weighed 77.1 Kg and whose height was 168 cm, had a mild case of diabetes. He was admitted to the hospital on June 10, 1927, with an infected foot which was incised and drained. He was discharged from the hospital on July 28, 1927, and reported to the outpatient department regularly. The diabetes was controlled with diet. He was readmitted to the ward on Aug 30 and Sept 2, 1927, for the studies on the respiratory quotient.

TABLE 1—Results of Studies on the Respiratory Quotient in Case 1

Time	Blood Sugar, Mg	Urine, Dextrose, per Hour, Gm	Expired Air			Oxygen Intake per Hour, Liters	Respiratory Quotient	Total Calories per Hour	Calories from Oxidation of Carbohydrate per Hour
			10 Minute Volume, Liters	Carbon Dioxide, per Cent	Oxygen, per Cent				
Aug 30									
8 00	85	0							
8 50			53.2	3.29	16.87	13.66	0.759	64.7	9
9 00	Given 35 Gm		of dextrose by mouth						
9 30	152								
9 45			57	3.31	16.96	14.26	0.784	68.1	15.6
10 00	176	0							
10 30			63.3	3.32	17.09	15.19	0.820	73.3	26.4
11 00	166	0							
11 15			57.8	3.19	17.24	13.32	0.819	64.3	22.5
11 45			57.9	3.22	17.20	13.52	0.817	65.2	22.1
12 00	140	0							
Dextrose burned in three hour period after meal of dextrose = 15.6 Gm									
Sept 2									
8 10			54.7	3.26	16.98	13.62	0.775	65.0	13
8 20	98	0	Given 80 mg of synthalin by mouth						
9 00			Given 35 Gm of dextrose by mouth						
9 20			58.8	3.32	17.06	14.28	0.811	68.7	22.7
9 30	118								
10 00	131	0							
10 15			68.1	3.13	17.67	13.56	0.931	67.4	49.2
10 45			67.8	3.11	17.56	14.10	0.886	69.2	40.8
11 00	65	0							
11 15			66.3	3.11	17.57	13.73	0.890	67.4	40
11 45			60.4	3.09	17.45	13.08	0.846	63.6	28.6
Dextrose burned in three hour period after meal of dextrose = 25 Gm									

CASE 2—H R, a man, aged 66, who weighed 69 Kg and whose height was 178 cm, had a moderately severe case of diabetes, he had been treated for this condition since 1922. The patient had had many admissions to the hospital, and at the time the studies on the respiratory quotient were made he was employed as an orderly. An apparent cirrhosis of the liver and an old pulmonary tuberculous lesion were present, which later became active and from which he recently died. At the time the studies on the respiratory quotient were made, the diabetes was controlled with a prescribed diet and from 25 to 30 units of insulin daily.

CASE 3—J I, a man, aged 23, who weighed 59 Kg and whose height was 184 cm, had a moderately severe case of diabetes. He required a prescribed diet and from 25 to 30 units of insulin daily. He had noted the symptoms of diabetes only three months previous to the present examination. He was admitted to the hospital on Sept 1, 1927, and discharged to the outpatient department on Oct 10, 1927. He received from 25 to 30 units of insulin daily with a prescribed diet until synthalin therapy was substituted, which was maintained until the diabetes was controlled by diet alone. He has since taken some insulin.

TABLE 2—Results of Studies on the Respiratory Quotient in Case 2

Time	Blood Sugar, Mg	Urine, Dextrose, per Hour, Gm	Expired Air			Oxygen Intake per Hour, Liters	Respiratory Quotient	Total Calories per Hour	Calories from Oxidation of Carbohydrate per Hour
			10 Minute Volume, Liters	Carbon Dioxide, per Cent	Oxygen, per Cent				
Aug 26									
8 00	115	0							
8 50			43.9	4	15.58	14.04	0.740	66.4	4.6
9 00	Given 35 Gm		of dextrose by mouth						
9 30	203	0							
9 45			54.1	3.75	16.15	14.94	0.791	71.6	17.9
10 00	243	0							
10 30			51.6	3.51	16.84	13.92	0.814	67.1	22.1
11 00	185	0							
11 15			53	3.49	16.72	14.06	0.781	67.2	14.8
11 45			54.3	3.48	16.82	13.98	0.800	67.1	18.8
Dextrose burned in three hour period after meal of dextrose = 14 Gm									
Aug 29									
8 00	137	0	37.3	4.29	15.51	12.78	0.746	60.5	5.1
8 10	Given 60 mg		of synthalin by mouth						
9 00	100	0	42	4.25	15.65	14.04	0.756	66.7	8
9 15	Given 35 Gm		of dextrose by mouth						
9 45	129								
10 00			49.9	3.86	16.33	14.16	0.793	69.4	18
10 15	183	0							
10 45			42.8	4	16.04	13.20	0.768	62.8	11.3
11 15	200	0							
11 30			49.4	3.95	16.44	13.86	0.811	67.2	29.6
12 00			51.6	3.71	16.58	14.01	0.808	67.5	21.6
12 15	134	0							
Dextrose burned in three hour period after meal of dextrose = 13.5 Gm									
Sept 20									
8 00	124	0	Given 50 mg of synthalin by mouth						
9 10			58	3.01	17.17	13.82	0.748	65.5	6.6
9 20	142		Given 35 Gm of dextrose by mouth						
9 50	150								
10 05			60.9	3.19	17.23	14.03	0.820	67.7	24.4
10 20	157	0							
10 50			58.2	3.13	17.15	13.83	0.780	66.1	14.5
11 20	131	0							
11 35			62.2	3.17	17.21	14.48	0.806	69.7	21.6
12 05			61.4	3.13	17.17	13.79	0.865	67.3	35.7
12 20	122								
Dextrose burned in three hour period after meal of dextrose = 16.7 Gm									

TABLE 3—Results of Studies on the Respiratory Quotient in Case 3

[illegible]

CASE 4—H S, a man, aged 57, who weighed 54 Kg and whose height was 160 cm, had a mild case of diabetes. He was admitted to the hospital on July 18, 1927, and discharged on Aug 20, 1927. The diabetes was usually controlled by diet alone.

CASE 5—H L, a youth, aged 16, who weighed 67.4 Kg and whose height was 190 cm, had a severe case of diabetes. He required a prescribed diet and from 70 to 80 units of insulin daily, although he was occasionally suspected of cheating on his diet. He also had hyperthyroidism and indications of other endocrine dysfunction. At the time of the experiments, his basal metabolic rate was plus 30 to 35. He had had numerous admissions to the hospital.

TABLE 4—Results of the Studies on the Respiratory Quotient in Case 4

Time	Blood Sugar, Mg	Urine, Dextrose, per Hour, Gm	Expired Air			Oxygen Intake per Hour, Liters	Respiratory Quotient	Total Calories per Hour	Calories from Oxidation of Carbohydrate per Hour
			10 Minute Volume, Liters	Carbon Dioxide, per Cent	Oxygen, per Cent				
July 26									
8 00	91	0							
8 45			43.5	3.27	16.89	11.11	0.758	52.8	6.9
9 10			Given 125 Gm of dextrose by mouth						
9 20	134	0							
9 40	217								
9 55			49.1	3.28	16.90	12.53	0.762	59.5	8.9
10 10	303	1							
10 25			55.1	3.24	17.17	12.95	0.816	62.5	21.3
10 55			60.5	3.26	17.10	14.51	0.805	69.8	20.9
11 10									
11 25	251	7.3	52.1	3.25	17.24	11.98	0.838	58.1	24.4
11 55			54.2	3.18	17.39	11.90	0.857	58	27.8
12 10	150	1.9							
Dextrose burned in three hour period after meal of dextrose = 13.7 Gm									
Aug 19									
8 00	102	0	Given 40 mg of synthalin by mouth						
8 45			42.4	3.65	16.67	11.29	0.813	54.3	18.7
9 00		0	Given 125 Gm of dextrose by mouth						
9 30	129								
9 45			52.7	3.10	17.58	10.88	0.889	53.4	32
10 00	183	0							
10 15			55.5	3.27	17.52	11.55	0.931	57.3	41.8
10 45			55.8	3.16	17.68	11.02	0.948	54.9	43.9
11 00									
11 15	109	0	53.6	3.23	17.47	11.39	0.901	56.1	35.2
11 45			53.7	3.25	17.54	11.12	0.930	55.1	40.2
12 00	100	0							
Dextrose burned in three hour period after meal of dextrose = 27.5 Gm									

CASE 6—E B, a man, aged 38, who weighed 67 Kg and whose height was 175 cm, had a moderately severe case of diabetes. He had noted the symptoms for about six months. He required a prescribed diet and approximately 35 units of insulin daily to control the diabetes. There were some indications of a slight hyperthyroidism.

#### COMMENT

The dextrose tolerance, as measured by the sugar in the blood and urine after a meal of dextrose, was notably improved during the period in which synthalin was given to the two patients with mild cases of diabetes, cases 1 and 4. In case 3, although the blood sugar curve was similar to that of the control subject, there was a marked decrease in urinary sugar. When the test was repeated a day later, without the use of any drug in the interim, the height of the blood sugar curve was much

decreased, although the respiratory quotients were similar to those during the control period. The patient in case 5 did not show any improvement in tolerance. The patient in case 2 showed a slight improvement with the use of synthalin, and a marked improvement three weeks later,

TABLE 5—Results of Studies on the Respiratory Quotient in Case 5

Time	Blood Sugar, Mg	Urine, Dextrose, per Hour, Gm	Expired Air			Oxygen Intake per Hour, Liters	Respiratory Quotient	Total Calories per Hour	Calories from Oxidation of Carbohydrate per Hour
			10 Minute Volume, Liters	Carbon Dioxide, per Cent	Oxygen, per Cent				
Sept 14									
8 00	157	0							
8 45			94.4	3.38	16.59	26.11	0.724	122.8	1.2
9 00		0	Given 33 Gm of dextrose by mouth						
9 30	234								
9 45			88.8	3.39	16.61	24.46	0.729	115.3	3.4
10 00	243	5.7							
10 30			82.4	3.56	16.32	24.25	0.716	114.2	0
11 00	251	9.8							
11 15			83.7	3.34	16.50	23.80	0.696	116.4	0
11 45			89.7	3.32	16.63	24.65	0.716	115.9	0
12 00	203	5.6							
Dextrose burned in three hour period after meal of dextrose = 0.8 Gm									
Sept 16*									
8 00	183	0							
8 50			65.3†	4.40	15.48	22.53	0.758	107	14
9 00	193	0	Given 33 Gm of dextrose by mouth						
9 30	243								
9 45			85.9	3.79	16.41	24.38	0.792	117.1	30.4
10 00	268	6.5							
10 30			84.7	3.35	16.75	22.46	0.748	106.5	9.5
11 00	224	6.2							
11 15			78.1	3.74	16.28	23.01	0.753	109.1	13
11 45			87.3	3.65	16.25	26.03	0.726	122.6	3.6
12 00	203	5.7							
Dextrose burned in three hour period after meal of dextrose = 11.8 Gm									

\* Previous to the experiment made on September 16, the patient was given synthalin as follows: September 15, 12 noon, 20 mg, 4:30 p. m., 30 mg, 12 midnight, 20 mg, September 16, 8 a. m., 30 mg.

† The low ten minute volume was due to the leaking of the valve on the spirometer side causing some rebreathing.

TABLE 6—Results of Studies on the Respiratory Quotient in Case 6

Time	Blood Sugar, Mg	Urine, Dextrose, per Hour, Gm	Expired Air			Oxygen Intake per Hour, Liters	Respiratory Quotient	Total Calories per Hour
			10 Minute Volume, Liters	Carbon Dioxide, per Cent	Oxygen, per Cent			
8 00	224	2						
9 05			57.8	3.71	16.41	16.51	0.771	78.6
9 15			Given 60 mg of synthalin by mouth					
10 00			58	3.63	16.41	16.54	0.756	78.6
10 15	197	2.5						
11 00			62.3	3.41	16.72	16.61	0.769	78.9
11 15	166	2.6						
11 35			65.5	3.24	16.85	16.99	0.741	80.3
12 10			63.9	3.34	16.83	16.52	0.766	78.7
12 15	180	1.5						

although these data are vitiated by the long interval between the tests during which time the patient received synthalin daily.

In four of the five cases, there was an increase in the respiratory quotients during the periods in which synthalin was given, over those during the control periods, indicating that more carbohydrate was being

utilized after the patient had been given synthalin. This increase amounts to from 10 to 15 Gm. of carbohydrate in the three-hour period studied. The patient in case 2 did not show this increase in utilization, although the diabetes was controlled for a number of weeks by diet with the aid of synthalin. It is important to consider the rate of ventilation in these experiments, as overventilation may easily increase the amount of carbon dioxide loss from the body and give a misleading high respiratory quotient. A comparison between the period in which synthalin was given and the control period of the average volume of expired air in the ten minute periods after the meals of dextrose had been given gives data which indicate that the higher respiratory quotients during the periods in which synthalin was given were not due to overventilation. This is possibly not true in the patient in case 3, whose rate of ventilation was appreciably higher during the period in which synthalin was given, and which was rather irregular throughout the experiments. In case 4, the results might seem to lose their significance because of the long interval between the control experiment and the experiment with synthalin. However, this case was used in a similar experiment on the respiratory quotient with another drug shortly before the study with synthalin. The results are not recorded in table 3, but they showed data on the sugar tolerance and the respiratory quotient similar to the control experiment.

Similar studies to those reported here have been made by A. Lublin.<sup>8</sup> He found in two rather severe cases of diabetes that after the patient had taken a meal of dextrose the respiratory quotient rose higher after previous synthalin therapy than in the control period when no drug had been given. In contrast to the present experiments, Lublin gave synthalin the day previous to the test, in one case 40 mg., and in the other 75 mg. In one patient (case 3) on whom we performed the test both immediately after he had received the synthalin and twenty-four hours later, we found a response of the respiratory quotient only in the former test while the latter was similar to that of the control period. In view of the reputed slower action of synthalin, it is surprising to note the quick response which was obtained in the present experiments.

Recent studies on the relation of synthalin to carbohydrate metabolism have been made by R. Bodo and H. P. Marks.<sup>9</sup> They were able to produce a marked hypoglycemia in rabbits, provided a sufficiently large dose was given parenterally. Rabbits killed during the time the hypoglycemia was present showed a decrease in the glycogen of the liver, which result is in contrast to the action of insulin. In the eviscerated cat from which the spinal column had been removed, and in the perfused

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8 Lublin, A. *Arch. f. exper. Path. u. Pharmacol.* **124**: 118, 1927.

9 Bodo, R., and Marks, H. P. *J. Physiol.* **65**: 83, 1928.

hind leg of a dog, the application of synthalin caused a disappearance of blood sugar. There was a decrease in the glycogen of the muscle, and respiratory experiments showed a decrease in oxygen consumption of the preparation. As the sugar which disappeared from the blood was neither burned nor stored, the authors sought another explanation for the phenomenon. The lactic acid of the blood was appreciably increased, and the respiratory quotients of the preparations rose above unity. These data suggest that the explanation of the mechanism of synthalin which reduces the blood sugar may be principally in the formation of lactic acid.

These experiments are of interest in relation to the present studies on the respiratory quotients. It might be possible that the apparent rise in the respiratory quotient after the administration of synthalin could be due to the formation of lactic acid which liberates carbon dioxide from the blood. If this was the case, it was thought possible that synthalin administered to a patient without dextrose would cause an apparent rise in the respiratory quotient. Case 6 was studied with this in mind. On the day previous to the experiment the patient was given 20 units of insulin at 7:30 a. m. and 5 units at noon, then the administration of insulin was discontinued, and synthalin was given as indicated in chart 6. Under these conditions the synthalin did not cause an increase in the respiratory quotient or a decrease in the consumption of oxygen. There was also no decrease in the consumption of oxygen in the other cases studied when the period in which synthalin was given was compared with the control period. The lactic acid of the blood in case 6 was determined before and after the administration of synthalin, and an appreciable increase was not noted. While the evidence is not at all complete, it would seem possible that the formation of lactic acid alone is not sufficient to explain the increase of the respiratory quotients in the present experiments.

Many investigators have considered the toxic action of synthalin on the liver, and mention has been made of its nephrotoxicity. We have certain data (being prepared for publication) which substantiate these views and emphasize the nephrotoxic action. We do not have any intention, in this paper, of advocating the use of synthalin as a substitute for insulin in the treatment of diabetes, but merely suggest that synthalin does have an insulin-like action on the respiratory quotient of the diabetic patient.

#### CONCLUSIONS

Synthalin, when given before a meal of dextrose, tends to increase the utilization of carbohydrate in the diabetic patient. This is indicated by an increase in the respiratory quotient during the three hours after a meal of dextrose when compared with a similar period before which synthalin was not given. The increase in utilization amounts to 10 or

15 Gm of carbohydrate during this period One patient failed to show such a response

Some of the patients responded to synthalin therapy by an increase in the tolerance for dextrose as measured by the sugar in the blood and urine

Because of accumulating evidence of the toxicity of synthalin for the human organism, the data in this paper are presented as suggestions for the mechanism of its action and are not to be interpreted as an advocacy of its clinical use

# THE REDUCING POWER (BLOOD SUGAR) OF FILTRATES FROM THE BLOOD OF THE RABBIT<sup>1</sup>

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Since the advent of insulin, the rabbit has been used so much for experiments which involve the determination of blood sugar that it seemed worth while to collect some of the material which has accumulated in our laboratory and treat it in such a manner as to reveal something of the behavior of the blood sugar in the normal animal.

The necessity of multiple observations seems to be generally accepted if one is to judge from the work appearing currently. As soon as multiple observations are made numerous problems arise, such as the number of observations which must be made before conclusions are warranted, the best manner of assembling observations so as to present the behavior of the series as a whole and at the same time give the reader a concrete mental picture of the behavior of the group, the constitution of the group of subjects, the effects of the nutritional condition of the subjects, whether or not the time of year or the time of day at which the observations were made affects the results, and so on. It is the purpose of this paper to present the results of a study of the importance of some of these factors in work on the blood sugar of the rabbit.

## A NORM FOR THE BLOOD SUGAR OF THE RABBIT

As the first step in the experimental part of the present study, it is sought to establish a norm for the blood sugar of the rabbit with a fair degree of precision. Shaffer and Hartmann's<sup>1</sup> method for the determination of sugar was used, with the conversion table of Duggan and Scott.<sup>2</sup> The blood was obtained from a vein of the ear. Petrolatum was always applied to the ear, and the blood was allowed to drop into a small dish containing a small amount of dry sodium oxalate in order to prevent coagulation. From this dish, the blood was drawn into a calibrated pipet from which it was measured into 7 cc. of water, and the protein precipitant was then added to the mixture. It was usually

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<sup>1</sup> Submitted for publication, Oct. 22, 1928.

<sup>2</sup> From the Department of Physiology, Columbia University.

1 Shaffer, P. A., and Hartmann, A. F. *J. Biol. Chem.* **45** 365, 1920-1921.

2 Duggan, W. F., and Scott, E. L. *J. Biol. Chem.* **67** 287 (Jan.) 1926.



necessary to use xylene to induce hyperemia and a freer flow of blood. The customary precautions to avoid excitation of the animal were observed.

Variation in the technic of analysis was insignificant in comparison with the physiologic variations encountered (table 1).

The usual value for  $\epsilon$  (Scott<sup>3</sup>) was of the order of 12 mg per hundred cubic centimeters of blood. Following the customary procedure of carrying  $\epsilon$  to two significant places when the first digit is less than 8 and reporting the individual results to the same decimal place, we would be warranted in reporting the results in milligrams. Since the indicated precision of the method is milligrams, this is the practice which has been followed in the tables. In view of the rather large mean deviation among the observations and of the deviation in the deter-

TABLE 1—Results of Multiple Determinations of Blood Sugar

Date	Animal	Condition	Blood Sugar Observed						$\epsilon$
11/19/23	Beef	Abattoir	87	89	89	94	99	92	$\pm 4.9$
	Rabbit	Normal	144 141	141 139	144 144	147 141	144 147	143	$\pm 2.5$
11/22/27	Rabbit 271	Normal	121	121	123	123	121	122	$\pm 1.1$
	Rabbit 262	Normal	126	123	123	121	126	124	$\pm 2.2$
	Rabbit 207	Normal	129	116	116	123		121	$\pm 6.2$
11/23/27	Cat	Ether	283 283	281 281	279 281	281 286	279 289	281	$\pm 2.5$
11/28/27	Cat	Ether	251	246	249	251		249	$\pm 1.9$
11/29/27	Rabbit 207	Normal	110	110	113	110	113	111	$\pm 1.1$
Mean $\epsilon$									2.8

minations per se as indicated in table 1, it is difficult to see just what the significance of the final place would be. Accordingly, in making calculations it has been our usual practice to round off the values to even multiples of 5. This greatly facilitates the process of calculation and can introduce no interpretative error. In cases in which the result was just midway between two multiples of 5, the nearest even multiple was chosen. Thus 122.5 and 117.5 would each be treated as 120.

All of the determinations reported in this series were made by a single analyst. In some instances, the observations reported were isolated, while in others they were the initial observations in the studies on the blood sugar curve. In the latter case, the specimen of blood which was used in the study was taken just before the administration of insulin or of sugar. When only one specimen was drawn, the observations were not repeated at intervals of less than one day, except in an insignificant number of cases. When the animals were subjected to further experimentation they were allowed at least one week for recovery.

The animals were obtained from a dealer in the open market and were not especially bred for uniformity. Had this been done there is little doubt that greater precision would have resulted (Riddle and Honeywell<sup>4</sup>).

We had found by previous experience that rabbits could be kept in good condition for long periods on a mixed diet of oats, hay and cabbage. This diet was used throughout the time in which these data were collected. The specimen of blood was drawn just after the animals were removed from the pens where they had free access to both food and water. This method was followed because it was thought that the condition more nearly represented the normal (in the sense of usual) condition of the animal than would that which existed after a period of inanition. Later in this paper the possible advantage in precision which may be gained by subjecting the animals to a short period of inanition before the specimen of blood is taken will be discussed. The data were collected over a somewhat prolonged period—from December, 1924, to August, 1927—as well as from a somewhat heterogeneous group of rabbits. No doubt these facts tend to increase the variations in the results but, at the same time, they make the results more representative of the general field. If variation in different animals and from time to time in the same animal is an intrinsic property of the blood sugar level in rabbits, this property cannot be made evident nor its causes worked out by establishing such artificial conditions as to eliminate it. It is true that there may be times when it is necessary to obtain the greatest possible precision, as in the assay of insulin, but care must be exercised as to the relation of this precision to the value of generalizations based on such experiments.

The series consists of 1,625 observations made on 215 rabbits. The results are published seriatim in table 2, and some of the general properties of the series are shown in chart 1. There was no selection or omission other than that necessary to make the series conform to the description in the preceding paragraphs.

As the rabbits were purchased in the open market, we did not have a record of their ages, but apparently they were in early sexual maturity when they were received. With few exceptions they were not used in this research longer than three months, although eleven were in use for periods varying from five to nine months, one for one year and nine months and one for two years and three months. In none of those used for the longer periods was there any consistent or progressive change which could be attributed to advancing age.

As the rabbits increased in weight during their stay in the laboratory, any possible relationship between body weight and blood sugar level

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<sup>4</sup> Riddle, O., and Honeywell, H. E. *Am. J. Physiol.* **67**: 317 and 337, 1923-1924.

TABLE 2—*Results of 1,625 Observations on 215 Rabbits*

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33			
123	128	122	122	96	130	125	122	112	112	116	91	105	160	112	136	121	136	123	118	121	131	102	97	134	124	113	123	131	126	130	121	131			
138	130	118	118	116	128	116	125	108	122	114	112	112	125	128	128	118	102	136	113	121	134	99	110	141	123	118	107	125	120	131	130	126			
128	111	114	114	93	140	128	102	132	130	94	135	105	116	114	149	126	105	131	121	113	105	105	115	124	118	121	118	110	139	113	121	130			
116	128	128	122	128	128	145	108	130	116	114	148	149	128	125	147	129	123	113	118	141	107	113	118	131	123	123	123	113	121	139	121	136			
102	125	128	119	128	108	102	132	108	106	105	80	145	128	148	144	126	134	110	126	118	107	94	126	121	136	123	123	107	120	121	118	136			
112	128	124	112	130	122	128	125	112	128	130	102	125	112	112	121	116	116	113	152	118	105	107	121	118	116	116	113	118	121	129	121	139			
111	135	124	116	122	92	142	119	112	128	157	91	125	122	119	110	123	123	118	118	126	89	121	130	106	123	107	129	130	131	121	136	131			
112	125	116	112	119	128	151	91	122	154	128	122	145	138	122	110	123	121	118	111	136	134	110	118	130	141	131	144	145	113	129	129	131			
102	125	124	110	112	142	116	118	148	160	135	110	135	122	110	133	121	118	111	136	134	110	106	113	110	110	110	139	129	107	123	126	136			
112	150	121	123	130	110	116	122	118	142	135	145	135	125	139	135	129	118	117	116	116	99	129	107	129	126	136	132	121	135	126	113	129			
116	154	112	122	102	116	112	132	116	160	140	122	130	130	142	123	105	118	118	105	113	110	110	129	126	136	136	132	121	135	126	113	129			
112	122	114	141	112	138	119	132	111	122	125	138	135	116	128	107	118	116	118	105	113	110	110	129	126	136	136	132	121	135	126	113	129			
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102	108	130	112	130	128	112	102	105	148	130	125	128	122	122	122	118	123	144	109	121	139	105	118	122	136	136	132	121	135	126	113	129			
122	119	128	130	114	108	119	140	132	132	125	116	125	119	116	123	105	118	121	107	102	110	97	102	126	141	123	129	127	131	136	118	113	136		
116	119	116	140	119	112	122	130	116	138	151	105	114	123	136	134	116	123	110	131	116	116	116	113	126	129	131	118	118	126	113	118	126	136		
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118	142	116	114	110	108	128	138	116	140	128	119	132	119	131	118	125	118	129	110	134	141	129	117	121	126	141	123	129	127	131	136	118	113	136	
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116	140	108	142	116	135	112	130	129	128	135	99	142	145	121	118	110	121	129	107	113	94	123	134	123	129	118	121	129	136	129	118	126	136		
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114	142	128	122	128	128	122	154	128	132	96	102	140	125	134	123	110	105	121	105	105	107	123	105	113	113	118	134	139	129	118	126	113	123	131	136
118	111	138	130	108	132	120	138	142	119	122	114	130	140	144	129	113	107	167	107	105	107	123	105	113	113	118	134	139	129	118	126	113	123	131	136
130	123	114	125	112	142	116	128	168	138	138	102	125	142	139	111	136	113	118	123	116	139	99	136	112	120	97	121	129	123	123	123	123	123	131	136
132	116	108	128	112	116	125	168	122	160	166	110	154	122	134	130	116	110	139	116	113	121	102	129	94	118	113	123	136	118	126	116	126	116	126	136
128	140	122	125	128	116	102	166	138	154	154	140	142	132	97	105	123	105	118	134	107	126	116	126	99	116	121	130	134	123	121	121	121	121	121	121
130	128	108	116	116	140	122	166	119	138	154	140	142	132	97	105	123	105	118	134	107	126	116	126	99	116	121	130	134	123	121	121	121	121	121	121
119	138	105	128	112	138	116	166	119	138	154	140	142	132	97	105	123	105	118	134	107	126	116	126	99	116	121	130	134	123	121	121	121	121	121	121
122	132	112	116	105	132	140	116	112	110	119	114	122	116	144	116	131	105	111	105	107	118	94	97	139	115	113	129	110	129	113	139	118	129	129	129
119	130	125	122	84	96	122	151	160	110	130	99	128	128	129	125	118	121	111	105	107	118	94	97	139	115	113	129	110	129	113	139	118	129	129	
114	142	108	114	128	138	140	160	119	105	122	105	140	128	129	125	118	121	111	105	107	118	94	97	139	115	113	129	110	129	113	139	118	129	129	
110	114	116	110	124	124	102	170	138	105	122	105	140	128	129	125	118	121	111	105	107	118	94	97	139	115	113	129	110	129	113	139	118	129	129	
124	122	124	108	114	122	112	157	138	116	110	112	125	122	123	105	118	121	111	105	107	118	94	97	139	115	113	129	110	129	113	139	118	129	129	
128	130	122	110	117	134	116	168	119	105	122	105	140	128	129	125	118	121	111	105	107	118	94	97	139	115	113	129	110	129	113	139	118	129	129	
134	112	130	122	110	117	134	116	119	105	122	105	140	128	129	125	118	121	111	105	107	118	94	97	139	115	113	129	110	129	113	139	118	129	129	
134	112	130	122	110	117	134	116	119																											

might be thought to have a bearing on the effect of age. Should such a relationship exist it would be of interest of itself. Consequently, the correlation coefficient (1) between body weight and blood sugar for a series of 1,299 observations was calculated and found to be less than 0.08—certainly not a significant value.

Those animals which were in use for the longer periods were allowed considerable time for rest and remained in good condition. The one which was under observation for the longest time died from an undetermined cause during the summer, about two months after last having been used.

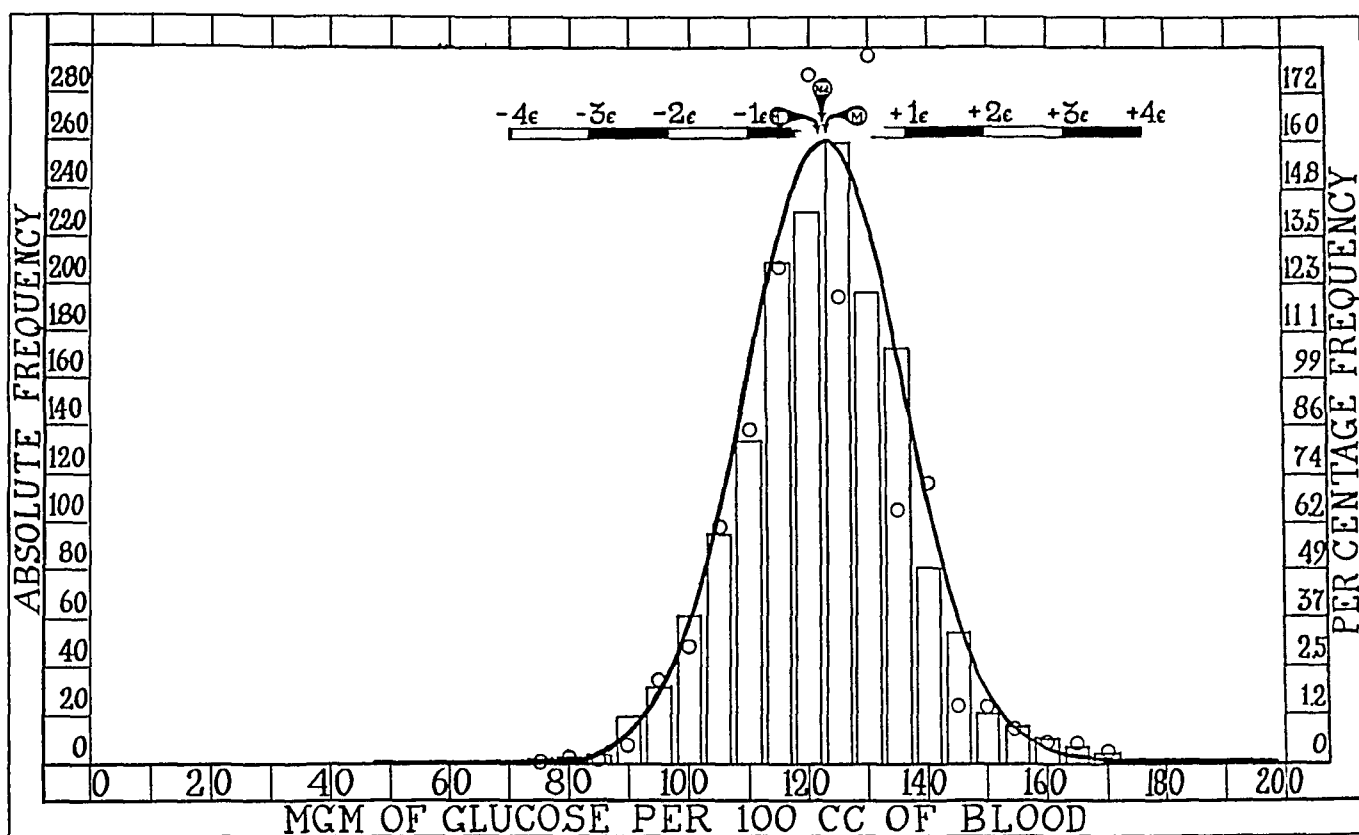


Chart 1—General properties of the 1,625 observations made on 215 rabbits

From the work of Riddle and Honeywell<sup>4</sup> on pigeons, it might possibly be expected that sex or the phenomenon of reproduction would also effect the blood sugar level in rabbits. So far our experience does not indicate that such is the case. Consequently, these factors have not been considered in the present paper. The problem, however, is of sufficient importance to warrant a special study, and it is hoped that our evidence may be presented in a later paper.

The possible effects of the season of the year or the time of day on the blood sugar level will be discussed subsequently. On the basis of the evidence presented these factors have likewise been disregarded.

As already stated, the series includes all of the observations that conformed to the conditions that have been outlined, which were obtained during the period of study. It results from this that observations were made on certain animals a great many times, while on the other hand there were 101 animals which were not used more than twice. In a later section argument is presented to show that there is probably a characteristic individual blood sugar level. From this, the possibility arises that the series has been biased by the inclusion of a large number of observations on certain animals with either a peculiarly high or low individual level.

In order to study this possibility, several subseries were selected from the grand series. These are presented (series 2 to 12 inclusive) in summarized form in table 3. The first of these series (series 2) consists of the initial observation on each animal. In this series there were 215 observations made on 215 different animals. Series 3, 4 and 5 consist of the first, second and third observation, respectively, on each of the 114 animals on which three or more observations were made. Series 6 is formed by combining series 3, 4 and 5. In doing this, a series is obtained which consists of 342 observations on 114 animals, three observations on each. In such a series there could not be any distortion due to individual peculiarities. All of the series, within the limits of expectation (Scott<sup>3</sup>), appear to be essentially similar in all of their properties to the grand series (table 3). It will be noted, however, that all of the observations were made early in the laboratory experience of the several animals, and that the means are all slightly below that of the grand series. The difference is less than  $3\epsilon_M$  and hence of itself cannot be considered as significant, but its persistence through all of these early observations might lead one to search for possible correlated factors. There are three apparent possibilities:

1. There may be a progressive rise of the blood sugar level associated with the advancing age of the animals. In view of what has been said this does not seem to be probable.
2. It may be that it so happened that the animals on which many observations were made had an unusually high characteristic blood sugar level.
3. It may be that continued use in the laboratory is associated with an increased blood sugar level.

In the series of 1,625 rabbits, twenty-five or more observations were made on each of thirteen animals. On each of eleven animals, twenty-five observations were made within a period of six weeks. The determinations were made on isolated specimens of blood drawn at approximately daily intervals, though determinations were usually not made on Saturday or Sunday and occasionally not on other days. The animals were not used for any other purpose during the course of these observations. The 275 observations on the eleven animals were

divided into five series of fifty-five observations each. The first five observations on each animal constituted the first series, the second five the second series, and so on through the group. The results are summarized in table 3. It will be seen that the characteristics for the 275 observations are essentially similar to those for the grand series. The mean for the first series of fifty-five rabbits (series 7, table 3), however, is unusually low, being only 118, while there is a progressive rise as the observations are accumulated (series 7 to 11, table 3).

As all of the animals were in early sexual maturity at the beginning of the period of observation, and as this was only of six weeks' duration it hardly seems probable that advancing age could have been a significant factor in bringing about this change in the blood sugar level.

TABLE 3—*Characteristics of Several Series of Blood Sugar Observations*

			Blood Sugar				
			M	E	FM	Md*	Mo†
2	Series of	215 initial observations	121	13.9	0.97	121	120
3	Series of	114 initial observations	121	12.8	1.20	121	121
4	Series of	114 second observations	121	14.4	1.35	121	121
5	Series of	114 third observations	121	14.6	1.37	121	121
6	Series of	342 first, second and third observations on 114 subjects	120	14.1	0.76	120	120
7	Series of	55 observations, being the first 5 observations on each of 11 subjects	118	10.4	1.40	117	115
8	Series of	55 observations, being the second 5 observations on each of 11 subjects	123	10.5	1.41	123	123
9	Series of	55 observations, being the third 5 observations on each of 11 subjects	125	10.2	1.33	125	125
10	Series of	55 observations, being the fourth 5 observations on each of 11 subjects	128	10.7	1.44	128	128
11	Series of	55 observations, being the fifth 5 observations on each of 11 subjects	128	10.5	1.41	127	125
12	Series of	275 observations, being the first 25 observations on each of 11 subjects	124	11.1	0.67	124	124
13	Series of	459 observations, curve 2 in chart 2	124	9.2	0.42	124	124
14	Series of	450 observations, curve 3 in chart 2	123	14.9	0.70	123	123
15	Series of	50 observations, curve 2 in chart 3	131	15.0	2.1	132	136
16	Series of	50 observations, curve 3 in chart 3	110	14.0	2.0	107	101

\* Md indicates the median

† Mo indicates the mode

Again, the animals in this particular group had a low rather than a high initial mean—118 as against 121 for all initial means or 120 for the first three observations for all animals on which three or more observations were made (table 3). It would appear from this that any bias due to individual characteristic levels would have been toward the lower rather than the upper limit. Apparently, the rise must be associated with the continued use in the laboratory. Just what is the determining factor is difficult to ascertain. So far our work does not offer an apparent clue. In the phenomenon, however, a variable is revealed which occasionally may have been overlooked in research work and which apparently may constitute a source of confusion in interpreting the results of a research. Controls should be so planned as to take account of this factor.

From all that has preceded, it seems fair to assume that the 1,625 observations, as shown in table 2 and chart 1, represent fairly the behavior of the blood sugar in rabbits that are fed, as it

exists during ordinary laboratory procedures, in which the animals are used repeatedly so long as they appear to be in good condition. When the observations are made early in the laboratory experience of the animals, a somewhat lower mean may be expected and a some-

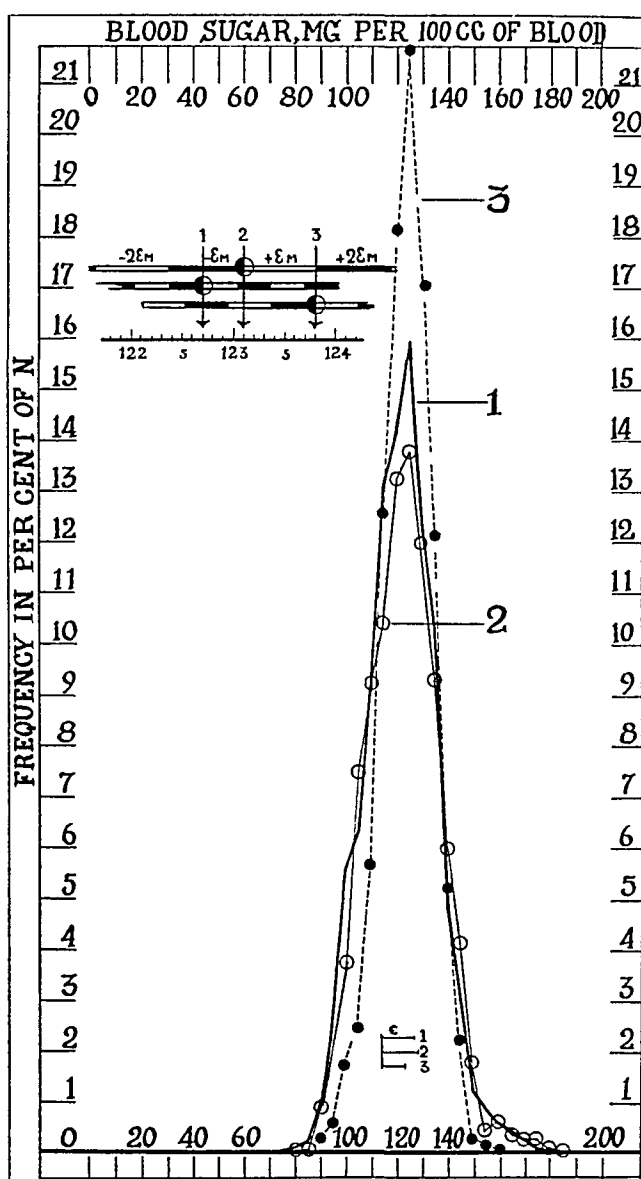


Chart 2—Curves for the three series of observations on the blood sugar of rabbits, showing the significance and importance of the characteristics of the series, as well as the method of comparison of the series by the superposition of the frequency curves. The insert shows that the 1,625 observations of the first series are not sufficient to separate this series from the others (Scott). It should be noted that the third series is almost as good because of the greater similarity of the material.

what higher one after the rabbits have been subjected to many determinations. The precision of the results will be somewhat enhanced if the

animals selected for observation in a particular research have been subjected to approximately similar amounts of experimental use

From work which is at present in progress in our laboratory, it appears that other properties of the series than the mean as  $\epsilon$  or the

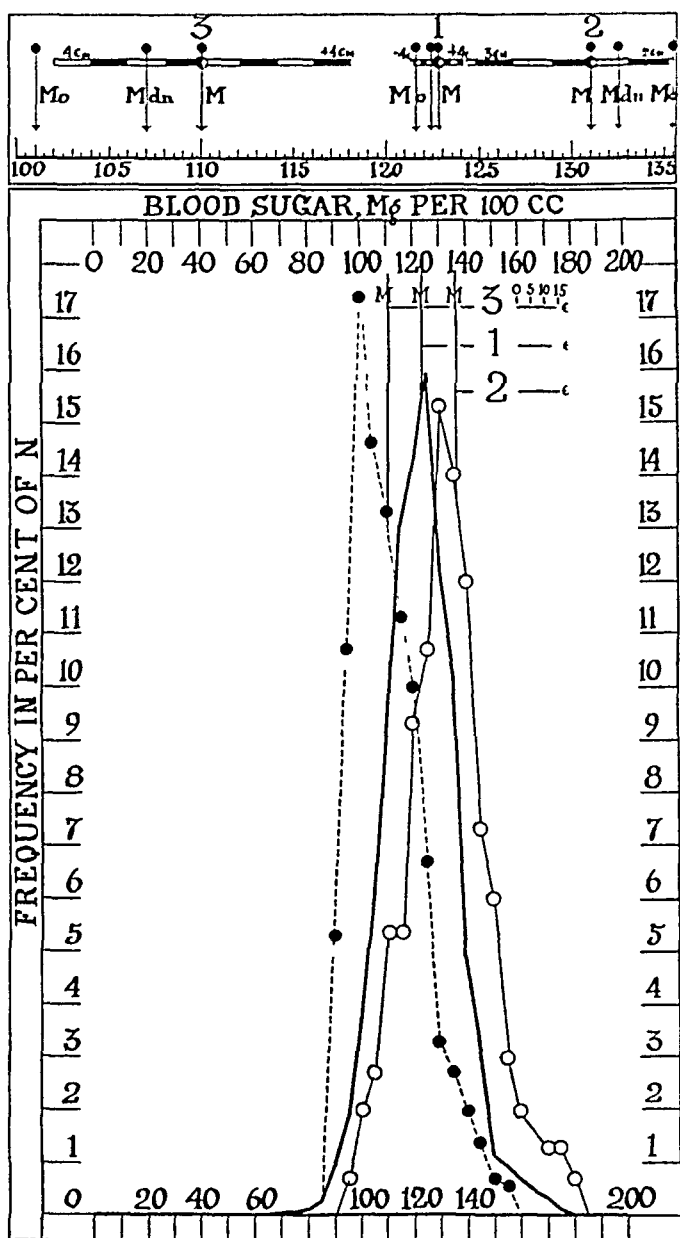


Chart 3—Curves for groups taken from the series of 1,625 observations to illustrate the fact that dissimilar means may occur in supposedly similar subjects

degree of skewness, may contribute information which aids distinctly in bringing out the significance of series which are being studied. For this reason it does not seem to be out of place to call attention to the behavior of some of these properties in a few series in which a considerable number of observations were made. The properties are better



shown by graphs than by the calculated values and hence charts 1 to 3 are introduced (also table 3)

In the series of 1,625 rabbits, 459 observations were made on an unusually uniform group of twenty-one rabbits within a period of about ten weeks. The results of 450 observations which were made on a rather heterogeneous group of 100 rabbits are also included. In the latter case, the period of observation extended over about three years. These two groups are natural in the sense that each resulted in the course of a specific research and they are mutually exclusive. No rabbit that was used in one appears in the other. As judged by the means alone, the results in the long series and in the two included series would have the same significance. The three series are shown in the form of frequency polygons in chart 2.

From this figure it will be seen that the data of the series of 459 rabbits do not cover the general field, and apparently it would be possible for a series with a limited range to misrepresent the center of the general field as well as the form of distribution, as is illustrated by the present case. We are not in possession of a series of this length in which such a misrepresentation has occurred, in chart 3, however, are shown frequency polygons for two series, each of fifty observations, which illustrate this possibility. The mean of each of these series differs from that of the series of 1,625 observations and from that of the other series by a significant amount as judged by the criteria of Scott,<sup>3</sup> which are considerably more severe than those in general use. All of the observations in these series are included in the series of 1,625 observations, and each is an integral series in which the original data were collected for a specific purpose other than that for which they are here used. As generalizations cannot legitimately be extended to populations other than that from which the data were drawn, it should be evident that too high a price may be paid for great precision. This is especially so if the precision is obtained by so close a selection of the subjects that they do not represent the field to which it is desired to extend the generalizations. The result may be true and, granted access to similar highly selected material, it may have a high degree of repeatability, but it may have such a limited significance that it is of little general value.

#### SEASONAL VARIATIONS

The question of seasonal variations is continually recurring (Riddle and Honeywell<sup>4</sup>) and if such variations exist in fact, it is a question of considerable importance for, aside from its intrinsic interest, it would be possible to compare only such series as were obtained at a corresponding time of the year or those in which the observations were distributed evenly throughout the year. The determinations on the series of 1,625 rabbits just considered were made at the convenience of the

observers and without regard to the reason. The result is that the observations were distributed somewhat roughly, but still distributed through the entire year. To these 1,625 observations were added 222 comparable observations which were obtained by other workers in the laboratory. All of this material was then grouped in two month intervals in the two combinations which are possible (chart 4).

As is to be expected, there is some variation from period to period, but it is by far too slight when measured by  $\epsilon_M$  to warrant the conclusion that it is related to seasonal conditions. The nature of the variations and their interrelationships in the two groupings, when corresponding periods of the year are compared, would bear out this conclusion. The observations, however, were not made for this specific purpose, and perhaps it may be best to leave the question open for the time being, remembering only that as it stands our evidence cannot be interpreted as indicating seasonal variation in the sugar of the blood of rabbits which are confined in the laboratory.

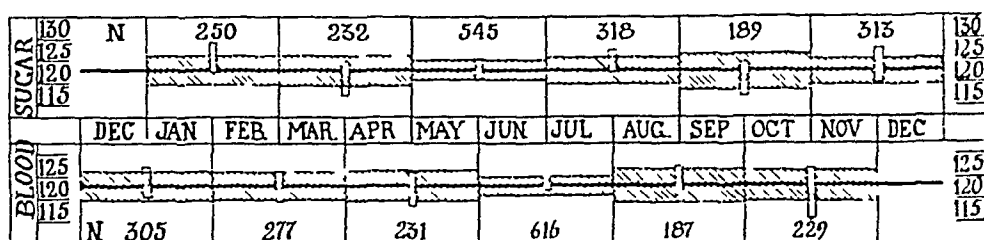


Chart 4—Seasonal variation of the blood sugar of the rabbit, 1847 observations distributed as indicated in the chart

#### DIURNAL VARIATION

Diurnal variation is also an important consideration in practical experimental work as well as of considerable interest in itself. Can it be presumed that, other things being equal, the blood sugar level is independent of the time of day? This problem has been attacked by various authors, notably by Eadie,<sup>5</sup> and usually answered in the affirmative. It was early noted by Macleod<sup>6</sup> later by Eadie as well as by others, that when specimens of blood are taken at short intervals, there is frequently a marked variation in the sugar content from specimen to specimen.

Since time progresses as the observations are accumulated, a progressive change in the blood sugar level may be and often has been interpreted as a diurnal phenomenon. Such a progressive change, however, might just as well be associated with the effect on the animal of

<sup>5</sup> Eadie, G. S. *Am J Physiol* **63** 513 (Feb) 1923

<sup>6</sup> Macleod, J. J. R. *Am J Physiol* **38** 415, 1915

TABLE 4—Results for Determination of Diurnal Variation \*

Rabbit	Sex	Body Weight		Blood Sugar										Characteristics of the "Individual" Series		
		Initial	Final	9	10	11	12	1	2	3	4	5	M	ε	εM	
				A M	A M	A M	M	P M	P M	P M	P M	P M				
270	M	2 36	2 23	110 134 155	137 121 134	130 144 118	126 139 131	113 145 121	123 129 113	141 129 129	129 110 126	131 131 136	129	11 3	2 2	
271	F	3 03	3 66	115 136 139	121 107 134	116 139 121	113 136 123	112 129 139	110 121 126	109 123 126	130 141 121	110 118 131	124	10 5	2 0	
273	M	2 59	2 70	149 121 136	118 117 126	119 110 123	118 126 118	97 129 126	94 123 121	123 131 121	122 126 129	127 121 131	122	10 6	2 0	
275	F	2 97	3 60	140 118 129	122 127 123	130 113 126	131 132 113	122 120 121	99 121 121	123 129 129	131 129 136	140 118 121	124	8 7	1 7	
277	F	2 35	2 60	129 121	142 121	126 136	113 139	118 118	121 123	110 118	136 121	131 123	125	9 0	1 9	
279	F	2 30	2 24	121 123	121 129	121 101	134 106	126 125	118 126	118 129	116 129	130 139	123	8 5	2 0	
281	M	1 85	2 31	110 107 123	131 131 123	104 129 129	130 123 129	121 136 134	141 126 129	126 134 131	139 136 139	123 121 123	127	9 1	1 8	
286	M	2 44	2 54	116 113 116	121 118 123	107 113 121	118 118 123	113 123 131	130 126 118	129 132 123	126 121 136	141 134 118	123	7 8	1 5	
288	F	2 42	2 06	123 110 113	136 123 121	121 107 121	109 116 116	106 126 118	117 121 139	123 123 113	121 126 121	113 113 129	119	7 9	1 5	
292	M	2 15	1 80	102 126	113 122	134 134	118 132	113 121	129 105	113 118	141 139	131 118	123	11 3	2 7	
294	M	2 15	2 61	124 131 121	105 113 131	140 129 139	120 135 131	118 134 118	116 141 131	136 129 123	124 113 129	127 126 126	126	9 0	1 7	
295	M	2 15	2 23	121	121	117	136	118	121	118	129	134	124	7 2	2 4	
296	M	2 67	2 56	118 131 118	126 127 118	131 126 123	135 126 129	116 131 126	123 123 123	118 118 113	126 131 126	132 127 131	125	5 6	1 1	
297	F	2 37	2 21	97 125	106 118	123 116	136 118	131 129	118 123	123 110	117 125	131 133	121	9 8	2 3	
298	M	2 36	2 62	106 134 131	130 110 121	131 123 113	129 134 121	129 119 129	129 139 118	121 116 139	102 110 118	129 129 134	124	9 9	1 9	
299	M	2 36	2 34	117 134 129	106 113 121	113 123 134	107 131 116	117 126 131	118 129 131	115 113 123	113 116 126	123 123 129	121	8 1	1 6	
300	M	2 20	1 60	121 103 126	119 110 118	107 120 118	129 118 121	124 121 126	118 129 136	114 123 118	107 118 118	121 123 121	120	6 5	1 2	
301	M	1 66	1 53	139	139	124	129	113	134	118	132	116	127	7 3	2 4	
302	M	2 55	2 45	97 129	118 131	121 136	121 126	129 134	131 121	131 136	139 139	118 121	127	10 2	2 4	
203	M	2 10	2 25	113 123	129 121	123 126	130 118	118 129	131 139	123 126	126 123	129 121	125	5 9	1 4	
205	?	2 37	2 35	131	126	123	131	131	121	136	131	134	129	5 0	1 7	
Characteristics of Series by Hours																
M				123	123	123	125	124	124	123	124	125				
ε				12	8	10	8	10	9	6	10	5				
εM				1 7	1 2	1 4	1 2	1 2	1 3	0 9	1 4	0 7				

\* In the table there were 459 observations, M = 124 ε = 9 1 εM = 4 2

drawing the specimens the hemorrhage glycemia of the older authors (Scott<sup>7</sup>) This phenomenon is illustrated in chart 6 and table 5

To determine whether or not there is a diurnal variation and at the same time to avoid any possible effects from taking consecutive specimens, the following experiment was devised Fifty-one determinations were made at each hour of the working day, that is, from 9 00 a m to 5 00 p m, inclusive An equal number of determinations was made on a given animal at each hour The rabbits were fed ad lib to one hour before the specimens of blood were drawn Water was allowed at all times Only one specimen was drawn from any particular rabbit on a given day The results are shown in table 4

From this table it appears that when the other conditions are maintained in as constant a condition as is practical, the blood sugar

TABLE 5—*Observations on Diurnal Variations at Two Hour Intervals for Twenty-Four Hours*

Rabbit	Blood Sugar												Characteristics of Series by Individuals		
	A M						P M						M	$\epsilon$	$\epsilon_M$
	1	3	5	7	9	11	1	3	5	7	9	11			
68	147	138	160	170	151	160	122	136	157	156	157	141	150	13.3	3.8
74	125	154	156	125	140	151	137	125	148	150	149	147	142	11.6	3.4
79	122	132	141	112	142	140	143	142	151	148	142	134	137	11.0	3.2
80	129	120	117	116	138	140	122	135	140	130	136	133	130	8.9	2.6
82	125	138	128	122	144	130	145	141	124	113	114	137	130	11.0	3.2
83	154	154	150	140	135	146	138	157	156	159	141	154	149	8.3	2.4
84	155	154	148	133	125	138	128	138	140	136	128	162	140	11.9	3.4
85	152	138	130	127	125	125	134	135	134	140	126	129	132	5.9	1.7
Characteristics of Series by Hours															
M	137	141	141	131	138	141	134	139	144	141	137	142			
$\epsilon$	14	12	15	15	9	11	8	9	11	15	14	11			
$\epsilon_M$	4.8	4.3	5.2	5.4	3.2	4.0	2.7	3.2	4.0	5.4	4.8	3.9			

level in the rabbit is independent of the time of day, at least during the ordinary working hours

Some years ago a short series of observations was made at two hour intervals throughout the twenty-four hours The series is not sufficiently long to warrant conclusions, but it does not seem probable that the opportunity of making a really adequate series will occur soon The data are therefore offered in table 5 at their face value and without comment except that they seem to be in harmony with the conclusion stated These animals had access to food and water throughout the period of observation

#### THE CONSTITUTION OF THE GROUP OF SUBJECTS

Animals have been found to vary among themselves in every character which has been studied from the point of view of such varia-

<sup>7</sup> Scott, E. L. Am J Physiol 34 271, 1914

tions There is no *a priori* reason to suppose that the characteristic blood sugar level is an exception to this rule. If the blood sugar level is not an exception, it would follow that a group of observations made on a single animal could not have as great a general significance as would the same number of observations each of which was made on a different animal. On the other hand, it might be expected that the series made on one animal would have the higher precision.

This was tested in various ways. Approximately 100 observations were made on each of three rabbits from about Dec. 1, 1924, to April 1, 1925, not more than one observation being made on any one day. These three series should be compared with another series (chart 5), they were made at about the same time, and the number of observations and subjects were equal.

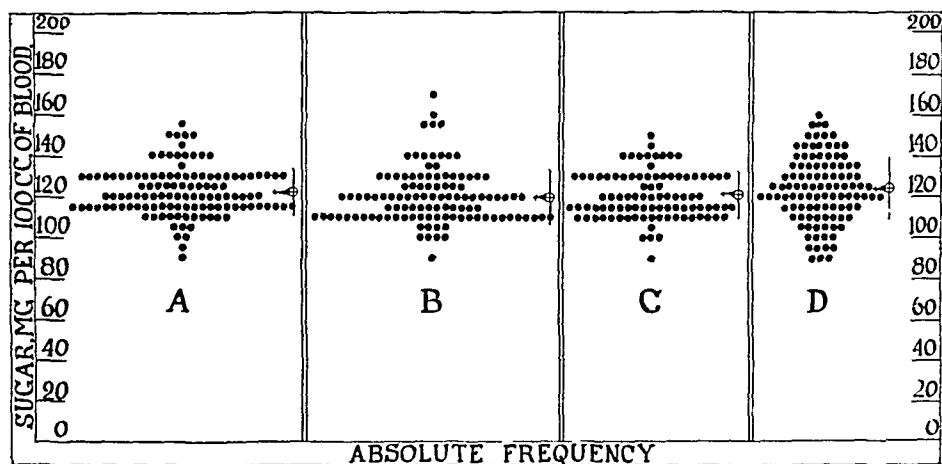


Chart 5—A study of the blood sugar of rabbits. The three series of many observations on one animal (A, B and C) should be compared with one series (D) of one observation on each of many animals. A, 117 observations on rabbit 84, made between Nov. 21, 1923, and April 1, 1924, B, 112 observations on rabbit 88, made between November 26 and April 1 of the same years, C, 92 observations on rabbit 94, made between December 7 and April 1 of the same years, D, 104 observations on 104 subjects made between November, 1923, and November, 1926. These observations were selected in such a manner that their value was without influence on the selection.

It is seen that a slight gain in precision is shown by the series which were derived from a single animal, but the gain is hardly of sufficient magnitude to be of practical value in drawing conclusions,  $\epsilon_M$ , for the "individual" series, being 1.2, 1.4 and 1.1 respectively, while for the heterogeneous series it was 1.6. Scott<sup>3</sup> gave 13.2 as the mean value of  $\epsilon$  for ten series of this number of observations made on heterogeneous groups of animals from which the mean value of  $\epsilon_M$  would be 1.3. The mean  $\epsilon_M$  for the foregoing three series is 1.2.

In the first series studied in the section on diurnal variation (table 4) twenty-seven observations were made on each of twelve animals. For the twelve animals the mean value for  $\epsilon$  is 88 while that for the nine series of fifty-one observations is 86. Strictly interpreted this would mean that there was actually a greater variation among the specimens taken wholly from a single animal than there was in the specimens taken from the mixed groups. The difference however is too slight to justify such a conclusion. In any case the data do not encourage one to expect any great gain in precision by the use of a single animal.

The means for the three rabbits studied in chart 5 do not differ significantly from those of an equal number of observations on a group of rabbits and so give no indications of the existence of a characteristic blood sugar level. Those shown in table 4, however are not so consistent. In this table the means of the mixed groups (vertical columns) are remarkably similar while those for the individual animals (horizontal lines) show considerable variation. The same condition is shown in another group in table 5. The number of observations made as shown in tables 4 and 5, is not so great as one would wish, but taken altogether the data appear to indicate that there are characteristic individual blood sugar levels which differ sufficiently to render data derived from different animals uncomparable and so vitiate conclusions based on such material unless the effect of the experimental condition is considerable.

Since a marked gain in precision cannot be expected by confining the observations to a single animal it would seem to be the better practice to include as many animals in the series as possible. The ideal would be to have the number of animals and observations equal (Pierce and Scott<sup>8</sup>).

#### CONTROL SERIES

All experiments should be accompanied by control observations which should be so made as to show the presumable behavior of the animal under the conditions which have been chosen as the standard and with which the response to the experimental conditions is to be compared. In studies on the blood sugar curve the usual practice is to make an initial observation just before the administration of the substance—insulin, dextrose, or what not—the effect of which is being studied. Is the initial observation of itself an adequate control? Can it be presumed that the second, third or fourth specimen would have been the same as the first had insulin for instance not been injected. Is it possible that the process of taking specimens or simply of the lapse of time might affect the result? Such an effect might be brought about

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8 Pierce, H. F. and Scott, E. L. Variation in Reducing Power (Sugar) of Normal Human Blood. *Arch. Int. Med.* **41**: 586 (April) 1928.

through excitement, discomfort or loss of blood to say nothing of less obvious factors (Scott <sup>7</sup>) If such an effect exists, the apparent reaction to the factor being studied might be masked or exaggerated depending on whether the two factors act in the same or opposite directions

Fifty observations were made in order to test this hypothesis In those observations the amount of 0.9 per cent of sodium chloride solution, which was used to carry 1 unit of insulin per kilogram of body weight but which, in this study, did not contain insulin, was injected into the animals Observations were then made three-quarters, one and a half, two and a half and three and a half hours after the injection The results are shown in chart 6

It will be noticed that there is a slight progressive rise as the number of specimens is increased This rise was noted previously by Scott and Ford <sup>9</sup> for rabbits, and for dogs by Hastings and Scott <sup>10</sup> It is true that the rise is not great and that possibly it may be neglected for

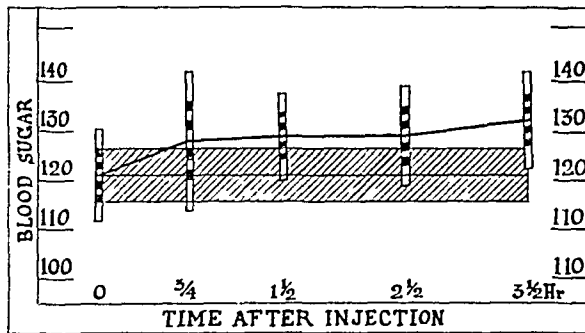


Chart 6—Experiment to show the effect of taking successive specimens of blood observed on the blood sugar

much work, but it should be noted that in every case it is significant as judged by Scott's <sup>3</sup> criteria, and it may be sufficient to explain the occasional apparent lack of effect of exceptionally small doses of insulin

In certain types of experiments it may be desirable to make the control observations at a time somewhat removed from the observations made under the experimental conditions Is such a practice justifiable? It has been shown that the variations exhibited by one animal may be as great as are those shown in a group of animals (tables 4 and 6) It follows from this that the blood sugar level of one animal cannot be considered to be constant from day to day It has also been shown (table 5 and chart 6, Macleod, <sup>6</sup> Eadie <sup>5</sup>) that similar variations occur from hour to hour In table 6 are shown the results in three groups of series In the first two groups three observations were made on each rabbit of a

<sup>9</sup> Scott, E. L., and Ford, T. H. *Am J Physiol* **63** 520 (Feb.) 1923

<sup>10</sup> Hastings, A. B., and Scott, E. L. *Proc Soc Exper Biol & Med* **17** 120, 1920

heterogeneous lot of fifty. In the third group six observations were made on each animal of a similar lot. The observations were then arranged in series, one observation on each animal appearing in each series. The first series for each lot contained the earliest observation

TABLE 6—*Observations on the Possibility of Individual Characteristics in Different Animals*

A				B				C						
Blood Sugar				Blood Sugar				Blood Sugar						
Rabbit	1	2	3	Rabbit	1	2	3	Rabbit	1	2	3	4	5	6
14	138	128	154	71	115	121	116	118	99	120	115	139	152	148
16	134	131	142	75	122	130	131	121	142	138	115	148	145	143
17	116	119	130	77	126	113	118	124	123	120	117	131	97	126
27	112	122	122	148	99	138	105	125	143	125	113	141	134	129
25	112	112	122	149	112	114	125	126	141	168	176	141	148	143
26	116	105	116	150	105	128	130	127	134	115	132	119	138	134
28	132	145	128	151	99	119	130	134	123	129	101	129	129	129
33	128	145	128	152	102	135	132	136	160	120	110	134	157	120
34	148	122	128	153	130	114	132	137	145	101	110	117	138	145
35	132	112	122	154	125	135	119	138	123	129	117	93	148	143
37	128	119	119	158	134	129	139	141	99	126	132	138	117	117
39	110	108	125	161	136	118	126	145	134	132	123	119	138	143
44	138	122	122	162	149	105	108	146	115	123	129	132	126	129
70	110	116	110	163	131	147	113	147	115	132	123	132	126	134
72	124	144	108	165	121	134	113	148	104	141	110	143	141	132
74	105	116	96	166	144	136	120	149	117	119	129	129	123	132
77	122	142	105	167	131	107	105	150	110	132	134	129	134	123
79	110	108	128	168	129	118	118	151	104	123	131	145	141	123
81	145	160	170	169	134	118	128	152	107	138	135	132	126	113
82	133	114	118	170	126	136	129	153	134	119	110	135	145	135
83	126	132	122	172	126	131	102	158	139	121	134	121	121	123
84	132	145	132	174	116	118	105	162	149	105	108	121	118	123
85	161	147	142	176	99	113	131	163	147	113	121	134	126	136
86	142	146	115	177	123	121	134	166	144	136	120	118	136	129
94	125	114	116	178	134	121	123	167	107	105	129	116	110	123
116	130	168	160	179	116	121	134	168	129	113	134	118	128	126
117	138	166	170	180	123	129	118	182	105	110	113	116	129	107
118	128	156	167	182	105	110	123	185	121	107	131	136	131	116
119	154	130	116	183	116	105	136	194	116	131	121	116	94	110
120	138	116	112	185	131	121	107	207	126	107	105	118	118	136
121	128	151	151	189	113	118	107	218	139	105	105	94	99	99
124	116	125	116	190	121	111	107	221	134	105	121	94	97	105
125	112	125	122	191	118	126	107	223	116	118	97	105	94	97
126	128	112	128	193	107	136	110	270	110	137	130	126	113	123
127	114	110	119	200	99	107	116	271	115	121	116	113	112	110
128	108	128	125	201	121	116	94	273	118	119	118	97	94	123
130	105	116	122	202	118	105	131	275	122	130	131	122	99	123
132	142	160	128	204	105	113	105	277	126	113	118	121	110	136
134	116	119	130	207	126	107	105	279	129	134	126	118	118	116
135	119	116	128	208	113	97	89	281	130	121	141	126	139	123
136	157	115	105	209	126	99	134	286	118	113	130	129	126	141
137	142	96	128	214	99	99	116	288	116	117	123	121	113	123
138	119	125	96	217	123	126	102	290	129	130	134	126	110	119
139	119	130	114	218	139	105	105	292	129	113	141	131	102	113
141	125	128	130	221	134	105	121	294	116	136	124	127	124	105
142	94	119	99	223	116	118	97	295	118	129	134	121	121	117
144	94	122	128	228	110	110	99	296	118	126	132	118	126	131
145	130	128	119	229	113	105	102	297	117	131	97	106	123	136
146	110	119	125	230	131	116	110	298	102	129	106	130	131	129
147	110	128	119	270	110	137	130	299	123	117	106	113	107	117
M	125	128	126		120	124	127		124	123	127	124	123	123
ε	15	16	17		12	16	17		14	12	12	13	16	12
εM	21	22	24		18	22	24		20	17	18	18	23	18

on the respective rabbits, the second series, the next consecutive observation, and so on through the group. There was no further selection of the observations. These groups are presented to show that while there may be considerable variation in the blood sugar level of the individual animals from day to day, the mean level of the group as a whole is



relatively stable (Pierce and Scott<sup>8</sup>) From this it would appear that one may presume the mean blood sugar level of an adequate series of observations made on a group of animals to be approximately constant from day to day and that, under these circumstances, the experimental observations need not follow the control observations immediately

It sometimes even occurs that it is undesirable or impossible to use the same animals for the control and experimental observations Figure 10 in the paper by Scott<sup>3</sup> illustrated the range within which the means of series of various lengths may be expected to fall When the effect of the experimental conditions is sufficient to throw the results widely outside of this range, conclusions may be drawn from such controls with the indicated degree of precision and without obvious objection It should be evident, however, that the experimental effect must be of considerable magnitude and that the conclusions must be distinctly guarded in their quantitative aspects

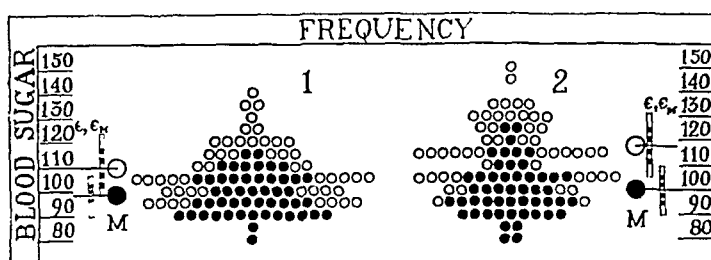


Chart 7—Two series to show the effect of a short period of inanition on the level and variability of the blood sugar of rabbits 1, the initials of series A, circles and after inanition , dots, 2, the initials of series B , circles, and after inanition , dots Circles, rabbits fed ad lib , dots, blood sugar after eighteen hours inanition Total length of bars  $\pm \epsilon$ , shaded portion  $\pm \epsilon_m$

#### INANITION

There is apparently a widely accepted agreement among workers in this field that a short period of inanition just previous to the drawing of the specimen of blood markedly increases the precision of the estimations on the blood sugar We sought to test this by the following experiments In the first there were two groups of fifty observations each In each group there were two series, in the first of which the animals received their accustomed food ad lib to the time of taking the specimen of blood, in the second series they were subjected to a period of eighteen hours inanition before the specimen was drawn The animals in one of these groups show rather low values in the series in which they were fed and this possibly may be related to the fact that there was some infection in this group of animals because of wounds which they had inflicted on one another in fighting, though the change is contrary in direction to that usually associated with infection While

this undoubtedly may affect the value of the series as a study of the effects of inanition on the level of the sugar it is not obvious that it would affect the variability, and so the series is included. From chart 7 it will be seen that inanition in both groups is accompanied by a distinct drop in the blood sugar level and that this drop is accompanied in each case by an increased precision as indicated by  $\epsilon$ .

In another experiment we sought to study the progressive effect of inanition over a period of twenty-four hours. These observations were made by a team of observers working in eight hour shifts and the results are consequently open to some objection, owing to the variable personal equations of the observers. The effect of taking successive specimens is also a factor that should probably be considered. All in all the design of the experiment is not of the best but as there is little

TABLE 7—*The Progressive Effect of Inanition on Blood Sugar During Twenty-Four Hours*

Rabbit	Elapsed Time in Hours												
	0	2	4	6	8	10	12	14	16	18	20	22	24
264	138	124	140	121	116	134	108	114	141	161	106	114	117
265	120	137	113	129	113	117	115	108	104	112	112	112	112
274	132	140	134	129	134	115	109	107	116	131	113	128	105
268	141	142	116	112	112	108	110	120	130	128	114	110	114
279	140	127	102	124	112	105	116	124	121	134	119	121	116
280	118	119	126	106	92	105	111	119	124	117	116	118	122
281	132	128	128	133	128	128	124	118	117	117	113	132	114
282	168	144	141	134	122	128	118	120	114	110	113	112	114
283	168	142	142	131	131	125	129	122	125	119	122	125	127
284	132	130	122	114	159	116	117	136	112	114	120	117	108
285	135	142	122	138	135	122	119	117	122	118	125	118	120
286	138	122	151	114	119	114	113	115	109	108	107	108	
M	138	133	128	124	122	118	116	118	120	120	115	118	115
$\epsilon$	16	9	14	10	17	10	6	6	11	9	8	7	6
$\epsilon M$	4.5	2.6	4.1	3.0	4.8	2.8	1.7	1.6	3.1	2.5	1.6	2.1	1.8

probability that the series will be carried to greater length in this form the data are given for what they are worth. In a general way they may be taken to indicate that the maximum precision is attained after about ten hours' inanition and that when once reached this precision is not much changed during the following fourteen hours. Apparently, the blood sugar level follows about the same time relations reaching its minimum at about ten hours, and is approximately constant from then to the end of the period studied.

Thus, the practice of subjecting the animals to a brief period of inanition with the purpose of increasing the precision of the results seems to be justified in the case of rabbits. Some unpublished work in our laboratory indicates just as conclusively that with cats and rats the reverse condition holds the greatest precision in these species being obtained with animals that have been fed. When the animals are subjected to inanition, it must be borne in mind that the observations were made under a special condition which cannot be called normal (usual)

and that conclusions based on such observations will have a correspondingly limited application. There is no evident reason why the practice of subjecting the animals to a short period of inanition should not be followed in the assay of insulin. Whether or not such a practice is permissible in other studies will depend on the object of the particular research. In any case the legitimacy of the practice is open to question and when used its justification is necessarily an integral part of the research.

#### SUMMARY

1 For a series of 1,625 observations, the mean reducing power (blood sugar) of rabbits that had been fed was found to be 123 mg per hundred cubic centimeters of blood with a mean deviation of 13. Some of the conditions which are or may be correlated with deviations in the reducing power of the blood and which possibly may lead to erroneous conclusions are discussed and illustrated.

2 The blood sugar seems to be independent of age, weight or sex, within the precision of the methods used.

3 It is probable that the reducing power of the blood of the rabbit is independent of the time of year provided that the animals are housed in the laboratory.

4 It also seems to be independent of the time of day.

5 It may be affected by the long continued use of the animals for such studies.

6 The use of many subjects in a research makes the general application of the conclusions based on the results more probable. On the other hand, many observations made on a single subject do not have a significantly greater precision and the research loses something of its general significance.

7 Some of the principles which determine a significant control were studied and methods for establishing such a control are discussed.

8 A short period of inanition causes a slight drop in the reducing power of the blood of the rabbit and rat. The variability of the results is decreased somewhat in the rabbit, while it is increased in the rat and cat.

# PANCREATIC FUNCTION

## III THE PANCREATIC SECRETION IN DISTURBED GASTRIC SECRETION <sup>2</sup>

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Since the investigations of Pavlov and his associates <sup>1</sup> in 1878, the mechanism of the pancreatic secretion has become of general interest. Pavlov reported that the pancreatic secretion is promoted by the entrance of the acid chyme into the duodenum, and not by the presence of that in the stomach. This stimulation of the secretion depends largely on the acidity of the chyme, for if a solution of 0.4 per cent hydrochloric acid is introduced into the stomach and rapidly discharged into the duodenum, a copious secretion of the pancreatic juice follows.

Popielski <sup>2</sup> and, independently, Wertheimer and Lepage <sup>3</sup> proved that even when all the secretory nerves of the pancreas are severed, the pancreatic secretion is promoted by acid. Popielski attributed this to a reflex, the center of which lies in the pancreas.

The classic experiments of Bayliss and Starling <sup>4</sup> showed in a striking way that in the action of dilute acid on the duodenal mucosa a substance, secretin, is formed, which can accelerate the flow of pancreatic juice even when all nervous connections with the secretory gland are severed. Starling further pointed out that, whereas in the mouth the reaction, which must be rapid, is entirely nervous, in the stomach the nervous mechanism is combined with the more primitive chemical mechanism. The nervous secretion preponderates in this viscus. He added further that in regard to the pancreas, the primitive chemical

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<sup>1</sup> Submitted for publication, Oct. 31, 1928.

<sup>2</sup> From the medical clinic of Prof. R. Inada, Imperial University of Tokyo.

1. Afanassiew, M., and Pawlow, J. *Beiträge zur Physiologie des Pankreas*, *Arch. f. d. ges. Physiol.* **16**: 173, 1878. Pawlow, J. *Weitere Beiträge zur Physiologie der Bauchspeicheldrüse*, *ibid.* **17**: 555, 1878.

2. Popielski, L. B. *Ueber die sekretionshemmenden Nerven des Pankreas*, Dissertation, 1896, cited by Bayliss.

3. Wertheimer, E., and Lepage, L. *Secretion pancréatique et atropine*, *Comp. rend. Soc. de biol.*, 1901, p. 759.

4. Bayliss, W. M., and Starling, E. H. *The Mechanism of Pancreatic Secretion*, *J. Physiol.* **28**: 325, 1902.

mechanism, namely, the formation of hormones and their circulation through the blood to the reactive tissue, suffices to account for the whole activity of the gland, and it is doubtful whether the nervous system plays any part in this activity

Pavlov and Fleig,<sup>5</sup> as well as Cohnheim and Klee,<sup>6</sup> proved that soap also is a vigorous stimulator of the flow of pancreatic juice. Bayliss<sup>7</sup> insisted that two mechanisms of pancreatic secretion exist, namely, chemical and nervous. Cohnheim and Klee proved that the administration of food itself stimulates the flow of pancreatic juice and bile similarly to the nervous stimulation of the stomach.

The estimation of the enzymatic activity opened a new era. In 1889, Boas asserted that the pancreatic juice is often detected in the stomach. Boldyreff<sup>8</sup> found that when oil is introduced into the stomach of dogs, a copious amount of the duodenal contents dashes into the stomach. In 86 per cent of his cases, Volhard<sup>9</sup> detected trypsin in the fluid removed from the stomach thirty minutes after the introduction of 200 cc of oil, while Faubel<sup>10</sup> was able to detect it in but 70.6 per cent.

Ehrmann and Lederer<sup>11</sup> collected the contents of the stomach forty-five minutes after the introduction of olive oil through a tube into the stomach and estimated the tryptic activity of the fluid separated under the oil. They found that in cases of achylia gastrica or in achlorhydria the tryptic activity is not only not diminished but in some cases is rather increased in comparison with that found in cases showing normal acidity.

Frank and Schittenhelm<sup>12</sup> also found trypsin in the regurgitation fluids in cases of achylia gastrica after oil was introduced.

Okada,<sup>13</sup> using the duodenal tube and estimating the tryptic activity of the duodenal return with the casein method, definitely proved for the

5 Fleig, C. Arch. gen. de med. **1** 1473, 1903.

6 Cohnheim, O., and Klee, P. Zur Physiologie des Pankreas, Ztschr. f. physiol. Chem. **78** 464, 1912.

7 Bayliss, A. Normale Pankreassekretion als Synthese von nervösen und humoralen Einfluss, Arch. f. d. ges. Physiol. **142** 531, 1911.

8 Boldyreff, W. Der Uebertritt des natürlichen Gemisches aus Pankreassaft, Darmsaft und Galle in den Magen, Arch. f. d. ges. Physiol. **121** 13, 1907.

9 Volhard, F. Ueber die Untersuchung des Pankreassaftes beim Menschen und eine Methode der quantitativen Trypsinbestimmung, Munchen med. Wchnschr. **54** 403, 1907.

10 Faubel, O. Untersuchungen über den menschlichen Bauchspeichel und das Fermentgesetz des Trypsins, Hofm. Beitr. **10** 35, 1907.

11 Ehrmann, R., and Lederer, R. Ueber das Verhalten des Pankreas bei Achylia und Anazidität des Magens, Deutsche med. Wchnschr. **35** 879, 1909.

12 Frank, F., and Schittenhelm, A. Vorkommen und Nachweis von Trypsin und Erepsin im Magen-Darmkanal, Ztschr. f. exper. Path. u. Therap. **8** 237, 1911.

13 Okada, S. Ueber die Pankreassekretion bei Sekretionsstörungen des Magens, Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo **13** 143, 1914.

first time that the flow of pancreatic juice is not necessarily unfavorably affected by disturbance of the gastric secretion, but rather that it is even accelerated in some cases

Using the same method as Okada and, in addition, estimating diastase following the procedure of Wohlgemuth, Hatta and Marui<sup>14</sup> also proved that the pancreatic secretion is not necessarily disturbed by disturbed gastric secretion

After investigations of the duodenal juice in subjects with disturbed gastric secretion the conclusions of Schoppe,<sup>15</sup> Isaac-Krieger,<sup>16</sup> Katsch and von Friedrich,<sup>17</sup> Roth and Sternberg,<sup>18</sup> Schoening,<sup>19</sup> Deloch,<sup>20</sup> McClure and his associates,<sup>21</sup> Nagai,<sup>22</sup> Kusnetzow and Michailowa<sup>23</sup> and others agreed in the main with those of Okada. It was pointed out, however, that the methods hitherto applied, i.e., the estimation of the enzymatic activity of the duodenal return, encountered theoretical as well as real objections when quantitative tests were considered. The presence of a considerable amount of saliva, gastric juice and biliary secretion so diluted the duodenal contents that a correct quantitative study of the pancreatic ferments was impossible. We have devised a

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14 Hatta, Z., and Marui, K. Ueber die Tätigkeit der Bauchspeicheldrüsen bei den Verdauungsstörungen des Magens sowie bei Aufnahme verschiedener Nahrungsstoffe und Arzneimittel, *Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo* **20** 121, 1918

15 Schoppe, W. Vergleichende Untersuchungen auf tryptisches Ferment in den Faces und im Duodenalsaft mit der Casein-Methode, *Arch. Verdauungskr.* **28** 289, 1922

16 Isaac-Krieger, K. Welchen Wert hat zurzeit die Untersuchung des Duodenalsaftes für die Diagnose der Darmkrankheiten? *Med. Klin.* **18** 431, 1922

17 Katsch, G., and von Friedrich, L. Bauchspeichelfluss auf Aetherreiz, *Klin. Wchnschr.* **1** 112, 1922

18 Roth, N., and Sternberg, F. Zur Frage der Pankreasachylie, *Deutsche med. Wchnschr.* **48** 1207, 1922

19 Schoening, 1922, cited by Roth and Sternberg (footnote 18)

20 Deloch, E. Zur Funktionsprüfung der äusseren Pankreassekretion durch Untersuchung des Duodenalsaftes, *Arch. Verdauungskr.* **30** 27, 1922

21 McClure, C. W., and Wetmore, A. S. Studies in Pancreatic Function. Enzyme Concentration of Duodenal Contents After Ingestion of Pure Foodstuffs and Food Mixtures by Normal Men, *Boston M. & S. J.* **187** 882, 1922. McClure, C. W., and Jones, C. M. Studies in Pancreatic Function. The Enzyme Concentration of Duodenal Contents in Pathological Conditions Involving the Pancreas, Liver and Stomach, *ibid.* **187** 909, 1922, Pancreatic Secretion in Man, Editorial, *J. A. M. A.* **80** 1145 (April 21) 1923

22 Nagai, K. On the Pancreatic Secretion in Achlorhydria Gastrica, *Nippon Naika Gakkai Zasshi* **10** 1211, 1923

23 Kusnetzow, N. W., and Michailowa, S. J. Die Sekretionstätigkeit der Bauchspeicheldrüse im Verlaufe von Erkrankungen der Digestionsorgane, *Arch. Verdauungskr.* **40** 41, 1927

new method (published in the first paper of this series <sup>24</sup>) which affords a reliable and accurate estimation of pancreatic function. Therefore, it might not be amiss to investigate this interesting problem further.

#### CLINICAL MATERIAL

The cases under consideration consist of an unselected group of seven cases of achylia gastrica and five cases of cancer of the stomach in connection with achlorhydria. Nine of the patients were men and three women. The cases of achylia gastrica were complicated by cholelithiasis, bronchial asthma, cardialgia and mild beriberi. In a woman, aged 29, with cancer of the stomach, the peritoneal cavity was involved with metastases and effusion. The scanty secretion and low enzymatic activity in this case were probably due to the extremely prostrated condition of the patient or to pancreatic involvement.

#### METHOD

The method employed in this investigation is the same as that described in the first paper of this series.

The results in three hour specimens of the duodenal contents shown in table 1 are presented in table 2.

In case 2 all of the enzymes as well as the bile pigment were extremely diminished, owing to the scanty amount of the juice obtained. In this case the achylia gastrica was complicated by peritoneal carcinosis with effusion, and the patient was extremely emaciated and prostrated, hence, the disturbed secretion of the pancreatic juice might be regarded as the consequence of this unusual condition. From the foregoing case, it is evident that the majority of cases of achylia gastrica and cancer of the stomach complicated by achlorhydria show normal enzymatic activity in the duodenal return, in some cases it is increased, so that the general average is higher than that in normal cases with undisturbed gastric secretion (we considered as a normal average 70 kilo-units for trypsin, 140 kilo-units for amylase and lipase in the first paper of this series). The average of bile pigment is also high, but it must be taken into consideration that most patients examined here were relatively old (eight were over 40 years of age). We found (as reported in the first paper) that the elimination of bile pigment increases with age.

In a study of the enzymatic activity, using the highest degrees found in frequent half-hourly or hourly determinations during three hours, we also found normal values in the main.

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24 Okada, S, Sakurai, E, Imazu, T, and Kuramochi, K. Pancreatic Function I. The Quantitative Estimation of Pancreatic Secretion, Arch Int Med 42: 270 (Aug) 1928.

TABLE 1—General Survey of the Data

Case Name	Sex and Age	Date	Stimu- lants Intro- duced into the Duodenum	Amount of Duo- denal Return in Three Hours, Cc	Degree of Enzymatic Activity												Tryp- sin in Three Hours Kilo- unit	Amyl- ase in Three Hours Kilo- unit	Lipase in Three Hours Kilo- unit	Bile Pig- ment in Three Hours Mg	Gastric Juice Free Hy- dro- chloric Acid Mg	Comment
					Trypsin			Amylase			Lipase											
					1	2	3	1	2	3	1	2	3									
					Hour Unit	Hour Unit	Hour Unit	Hour Unit	Hour Unit	Hour Unit	Hour Unit	Hour Unit	Hour Unit	Hour Unit	Hour Unit	Hour Unit						
1 K W	♂ 41	1/15/27 1/19/27 1/22/27 2/1/27	Alcohol Water HCl (0.2%) Ether	129.5 97.0 172.5 196.0	320 320 200 320	320 500 200 200	800 500 500 320	893 527 607 908	811 893 636 603	1,763 979 1,260 926	678 726 410 508	780 810 560 440	760 1,164 500 396	60.6 55.6 61.7 58.9	148.2 134.7 164.7 170.7	93.2 87.1 109.4 90.0	17.3 7.6 26.6 30.4	0 0 0 0	Achylia gastrica + cholelithiasis			
2 Y T	♀ 41	1/28/27 2/2/27	HCl (0.2%) Water	137.5 107.0	320 800	700 500	500 320	1,243 1,885	2,203 2,287	2,162 1,873	1,260 700	516 360	468 456	73.4 63.7	220.8 202.6	140.8 61.5	19.3 9.7	0 0	13 5	Achylia gastrica		
3 K W	♂ 20	3/19/27 4/26/27	No No	104.5 119.5	800 800 700 800	320 500 1,250 320 500	500 1,250 320 500	2,124 1,851 1,476 1,587	2,053 2,284 1,740 1,319	1,987 2,009 1,790 1,880	2,112 1,776 1,610 3,220	1,020 666 2,480 1,150	1,428 3,520 342 780	67.5 85.2	223.0 189.5	165.8 248.3	10.7 35.1	0 0	5	Achylia gastrica		
4 I T	♂ 20	8/30/27	Water	159.0	250	1,000	1,000	637	1,663	1,598	476	960	1,390	126.8	217.1	163.2	19.5	0	8	Achylia gastrica + beriberi		
5 K O	♂ 54	9/3/27	Water	195.0	320	320	320	918	1,085	804	1,900	1,100	1,400	62.8	185.7	272.6	23.6	0	8	Achylia gastrica + cholelithiasis		
6 H K	♂ 34	1/13/28	No	80.0	250 500	800 800	800 320	2,185 2,119	1,122 1,867	2,036 2,230	58 138	420 144	142 115	65.5	129.3	20.9	15.5	0	16	Achylia gastrica + bronchial asthma		
7 M T	♀ 61	1/25/28	No	88.0	320	250	500	1,221	1,639	1,543	1,188	262	1,210	46.4	128.6	95.8	5.3	0	7	Achylia gastrica + cardalgia		
8 M W	♂ 19	12/24/28	Alcohol	105.0	800 800	1,250 1,270 2,000	800 320 500	1,921 2,083	2,043 1,979	1,829 2,188	255 575	540 420	1,025 960	122.1	208.2	119.2	27.2	0	12	Cancer of the stomach		
9 Y O	♂ 54	3/5/27	Water	118.0	500	800	800	1,238	2,018	2,067	1,750	4,960	2,640	101.9	257.9	467.8	20.4	0	8	Cancer of the stomach		
10 K I	♂ 64	12/6/27	Water	195.5	50 200	500 500	800 500	984 1,183	1,810 2,197	1,833 1,694	185 680	1,560 1,860	1,775 1,600	63.9	286.1	198.1	11.9	0	10	Cancer of the stomach		
11 K A	♀ 29	12/23/27	No	15.0	800	500	500	2,530	1,859	1,740	230	170	110	9.5	52.0	3.4	0.5	0	12	Cancer of the stomach + peri- toneal adhesions		
12 K I	♂ 62	4/13/28	No	203.0	500	500	500	1,305	2,740	2,601	936	965	744	101.5	119.5	169.1	5.8	0	10	Cancer of the stomach		



From every point of view, we may conclude that the pancreatic secretion is not necessarily disturbed by disturbed gastric secretion. It is rather increased in some cases.

## COMMENT

We feel warranted in concluding that the pancreatic and biliary secretion is not disturbed as the consequence of disturbed gastric secretion. The foregoing observations suggest that the presence of hydrochloric acid is not necessary in order to stimulate normal pancreatic

TABLE 2—*Results in Thrice Hour Specimens of Duodenal Contents*

<b>Trypsin</b>			
Below 30 kilo units	1 case		
From 30 to 120 kilo units	9 cases		
More than 120 kilo units	2 cases		
Average of the whole (17 examinations)			99.9 kilo units
Average of the cases showing more than 30 kilo units			108.1 kilo units
<b>Amylase</b>			
Below 50 kilo units	1 case		
From 50 to 300 kilo units	10 cases		
More than 300 kilo units	1 case		
Average of the whole			272.5 kilo units
Average of the cases showing more than 50 kilo units			296.9 kilo units
<b>Lipase</b>			
Below 50 kilo units	2 cases		
From 50 to 300 kilo units	8 cases		
More than 300 kilo units	2 cases		
Average of the whole			161.3 kilo units
Average of the cases showing more than 50 kilo units			191.2 kilo units
<b>Bile Pigment</b>			
Below 5 mg	1 case		
More than 5 mg	11 cases		
Average of the whole			21.4 mg
Average of the cases showing more than 5 mg			25.1 mg

TABLE 3—*Data of Enzymatic Activity*

<b>Trypsin</b>		
Below 500 kilo units		1 case
More than 500 kilo units		11 cases
<b>Amylase</b>		
Below 600 kilo units		0
More than 600 kilo units		12 cases
<b>Lipase</b>		
Below 600 kilo units		2 cases
More than 600 kilo units		10 cases

secretory activity. We had had much experience in normal cases, showing that a profuse secretion of pancreatic juice occurred during fasting when the gastric content drawn simultaneously with the pancreatic juice by means of the gastric tube did not show an acid reaction. The secretin mechanism is generally accepted and no doubt plays a rôle in normal digestion, however, we are of the opinion that this mechanism has been overemphasized. The facts that secretin is detected in nearly the same concentration in two thirds of the small intestine and that the acid chyme soon becomes alkaline on entering the intestinal tract show that only a small part of this hormone

partakes in this mechanism. It is highly suggestive that some energetic and important mechanism, other than the secretin mechanism exists for promoting the pancreatic secretion. The evidence of this mechanism will be suggested in the fourth paper of this series.

#### CONCLUSIONS

The enzymatic activity of the duodenal return during three hours' collection was estimated. Evidence that the pancreatic secretion was disturbed as the consequence of disturbed gastric secretion was not found. On the contrary, there were cases in which an increased activity was detected, so that the general average of tryptic, amylolytic and lipolytic efficiency was much higher in comparison with that of normal gastric secretion. If one takes the highest value of hourly or half hourly specimens, the enzymatic activity was usually over the minimal normal limit. From these observations, it is evident that the presence of hydrochloric acid is not necessary in order to stimulate normal pancreatic secretory activity. The importance of the secretin mechanism seems to have been overemphasized. It is highly suggestive that some powerful stimulating mechanism other than that of secretin exists.

# COARCTATION OF THE AORTA

A CASE OF THE ADULT TYPE IN A CHILD SIX MONTHS OF AGE \*

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Coarctation is the term applied to the congenital stricture of the arch of the aorta below the origin of the left subclavian artery. This condition exists in two distinct forms as differentiated by Bonnet<sup>1</sup> the "infantile" and "adult" types, according to the morphology and, possibly, the etiology of the lesion. In the first group he places cases presenting a diffuse narrowing of the fetal isthmus of the aorta, which may be regarded as the persistence of the normal relationship before closure of the ductus arteriosus. In the "adult" type there is found a relatively abrupt stricture, even complete obliteration, at or in the immediate vicinity of the ligamentum arteriosum. The constriction often resembles that produced by a ligature around a vessel and has been (probably erroneously) termed nondevelopmental and attributed to postpartum extension of the tissue of the ductus into the wall of the aorta. This explanation was first advanced by Craigie<sup>2</sup> and has been known as the skodaic theory. As late as July, 1927, this theory was mentioned by Mackenzie,<sup>3</sup> in spite of its inapplicability in cases in which stricture coexists with more or less patency of the ductus itself, and in cases in which a membranous ridge is present at the inner aspect of the stricture. The more probable explanation was advanced earlier by Reynaud,<sup>4</sup> Rokitsky<sup>5</sup> and Loriga,<sup>6</sup> and emphasized by Hamilton and Abbott<sup>7</sup> in a recent paper, as being due to "a true abnormality of development arising in embryonic life in the descending limb of the

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\* Submitted for publication, Dec 12, 1928

† From the Pathological Laboratory of Harlem Hospital

1 Bonnet, L. M. Sur la lesion dite stenose congenitale de l'aorte, *Rev de med* 1903, vol 23

2 Craigie, D. Instance of Obliteration of the Aorta Beyond the Arch, *Edinburgh M J* 56 427, 1841

3 Mackenzie, G. M. Coarctation of the Aorta, *Am J M Sc* 174 87, 1927

4 Reynaud, A. Observation d'une obliteration presque complete de l'aorte, *Jour hebd de med* 1 161, 1828

5 Rokitsky-Dlouhy. Handbuch der speciellen pathologischen Anatomie, ed 3, 1856, p 337

6 Loriga, G. Stenosi ed oblitterazione congenita dell'aorta, *Riv clin di Bologna* 7 529, 1887

7 Hamilton, W. F., and Abbott, M. E. Coarctation of the Aorta of Adult Type, *Am Heart J* 3 381, 1928

primitive left aorta at the point of junction of the fourth, fifth and sixth arches of this side" In some measure of support of the latter theory, two cases of the "adult" type of coarctation present shortly after birth, are mentioned by them, the first from Ettlinger<sup>8</sup> in an infant 17 days old, and the second from Wadstein<sup>9</sup> in an infant aged 7 months The case we are reporting in this paper is another of the "adult" type of coarctation in a child, aged 6 months

#### REPORT OF CASE

*History*—P E, a boy, aged 6 months, born in the United States of Porto Rican parents, was admitted to the Harlem Hospital on July 26, 1928 The child left the Willard Parker Hospital eighteen days before, after having been under treatment there for diphtheria for the preceding two weeks A cough was noticed at the time he arrived home, the expectorated sputum being white and thick resembling curdled milk Two days before admission to our hospital, the child became extremely ill and was brought to the pediatric clinic, where treatment was prescribed, and he was sent home On the day before admission he refused to suckle, but since then he has taken a little nourishment by spoon His temperature had been high for the two days previous to admission He cried little, but his voice became weaker

He was born at the Lying-In Hospital in New York, on Jan 24, 1928, at full term, delivery being spontaneous He was breast fed up to the time he was taken to the Willard Parker Hospital and again after his return home He was an only child, the mother never having been pregnant before The mother and father were living and well

*Physical Examination*—The patient, a colored male infant, 6 months of age, was lying in bed in a comatose condition He had a rapid respiration, rapid, thready pulse and a high temperature He was obviously acutely ill The head was normal in size and shape, the posterior fontanel was closed, and the anterior fontanel admitted the tip of a little finger There were no craniotables The sclerae were clear, and the pupils pinpoint in size and fixed to light There was incoordination of the extrinsic eye muscles The ears and nose were normal The anterior pillars of the fauces were slightly injected, and the lips were cyanotic The neck flexed normally, and there were no abnormal pulsations or thrills The chest was normal in shape, except for Hutchinson's grooves The lungs were clear on percussion, but were full of loud subcrepitant râles heard both anteriorly and posteriorly Patches of marked bronchial breathing with increased voice sounds were present The heart sounds were obscured by the pulmonary signs The breathing was mostly abdominal There was moderate distention, but masses, tenderness and rigidity were not observed The extremities were normal There were no marked epiphyseal enlargements The reflexes were normal

The patient's temperature on admission was 105.2 F, the pulse rate 90 and the respiratory rate 50 The child died a few hours later Cultures of the blood and spinal fluid taken immediately after death, under sterile conditions, were negative after four days

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8 Ettlinger Zur Casuistik der angeborenen Herzfehler, Klin Wchnschr 19 399, 1882

9 Wadstein, E Stenos och obliteration af aorta vid eller i närheten af ductus botalli, Lund, 1897

*Autopsy*—The body was that of a colored male child about 6 months of age. It was fairly well developed but somewhat emaciated. Rigor mortis was complete sixteen hours post mortem. There were no signs of jaundice, edema or petechiae. The tonsils, thyroid and thymus were normal.

The chest was symmetrical. The pleural cavities did not contain any free fluid, and the pleura was smooth but dulled in appearance. The lungs were firm and airless practically throughout, with exception of the right middle lobe. On section, the lung tissue was a mottled dark red and gray, irregularly raised and granular in appearance. The blood vessels were normal. The left bronchus 1 cm from its bifurcation presented an area of necrosis on its walls, 4 mm in diameter. On opening this bronchus longitudinal fissures appeared in the necrotic area. A probe passed into these small artificial fissures pointed to the region of the ductus botalli. The connective tissue lying between the necrotic portion of the trachea and this same region was thickened and injected but did not contain any free pus. There was an abrupt marked stricture of the aorta directly at the point where it was joined by the obliterated ductus. The aorta was dilated slightly above and below the stricture. The circumference of the aorta at the aortic valve was 3.2 cm, at the widest part of the ascending portion, 3.1 cm, at the widest part of the arch, 3 cm, at the widest part just above the coarctation, 2.9 cm, at the coarctation, 0.66 cm, and at the widest part just below the coarctation, 2.9 cm.

The heart was enlarged, the pericardium was smooth and did not contain any excess fluid. The cardiac enlargement was due to moderate hypertrophy of the left ventricle. The valves were normal. The foramen ovale was patent. There was no increase in the size of the superior thoracic vessels, nor were other vascular anomalies present. The abdominal organs presented only congestion. The gastrointestinal and genito-urinary tracts were normal.

The diagnosis was bilateral confluent bronchopneumonia, coarctation of the aorta, localized necrosis of the left bronchus, and congestion of the abdominal organs.

#### COMMENT

The symptoms of coarctation when present are (1) dyspnea, usually not so marked as in other forms of congenital heart disease, (2) results of an unequal circulation with unequal pressure, such as headache and coldness of the lower extremities. Among the signs may be cyanosis, a loud precordial murmur, unequal pulse rates, weakness of the dorsalis pedis and visible pulsation in the upper part of the thoracic region. The x-ray picture may show an absence of the aortic bulge in the second left interspace. Other congenital cardiac lesions may accompany this abnormality. According to the severity of the lesion, a case will fall into one of the three following groups, as indicated by Hamilton and Abbott: (a) cases in which the condition is apparently entirely latent, (b) cases occurring in previously robust and vigorous persons, in the full tide of early adult life, in whom signs of cardiac insufficiency may suddenly set in as the result of what would otherwise be an inadequate cause, (c) a few cases in which signs of vascular or cardiac disability exist from early childhood.

It is difficult to state what part the anomaly played in the sequence of events leading to this child's death, since bronchopneumonia follow-

ing an acute infectious disease is a common enough cause of death in children. We may feel, however, that because of the absence of symptoms of cardiac disease before the initial illness and in view of the marked stenosis existing, this case probably fits into group b, although it is likely that had the child lived to an older age it would have fitted into group c.

It is interesting to note that cases of the 'adult' type of coarctation usually present only minor anomalies of the cardiovascular system. This is just the opposite of what is found in the "infantile" type. In our case the sole accompanying anomaly was a patent foramen ovale. There occurred, however, two of the three important secondary changes, though to only a mild degree: first, the moderate dilatation above and below the stricture, and second, the moderate hypertrophy of the left side of the heart. The development of a collateral circulation, the most striking of the secondary features, was entirely absent. In view of the degree of the stricture this may again be attributed to the age of the patient.

A further point of interest in the case is the significant position of the focal necrosis of the left branch of the bronchus in relation to the coarctation and the ligamentum arteriosum. It seems reasonable that the pressure of the blood stream through the narrowed lumen exerted sufficient traction on the ligamentum and the tissue surrounding it to have caused mechanical irritation of the adjacent bronchus and so provided a reason for the greater involvement of the bronchus at this point during the recent illness. The mechanism would be similar to that described in the production of traction diverticula of the esophagus. As a matter of fact, the traction of the ligamentum arteriosum, said by some to be one of the causes of coarctation, is believed to be the cause of the conical aneurysms produced in the wall of the aorta at this point.

#### SUMMARY

1 Coarctation of the aorta may be either "infantile" or "adult." The first term is applied to those cases presenting a diffuse narrowing of the fetal isthmus, the second, to those presenting a relatively abrupt stricture, varying in degree, in the vicinity of the ligamentum arteriosum.

2 A child, 6 months old, who was admitted with a bronchopneumonia of at least two days' duration, died some hours after admission. The developmental and family history was negative, but the infant had been ill with diphtheria and discharged from the hospital as cured eighteen days previous to admission. No cardiac signs were elicited on examination because of the masking signs of bronchopneumonia.

3 Autopsy revealed, in addition to an extensive bronchopneumonia, a localized necrosis of the left bronchus and a coarctation of the aorta.

of the "adult" type This was accompanied by a patent foramen ovale, a moderate dilatation above and below the stricture and a moderate hypertrophy of the left side of the heart

#### CONCLUSIONS

1 The focal necrosis found in the bronchus was probably initiated by the pressure of the blood stream flowing through a narrowed lumen and exerting sufficient traction on the ligamentum at this point to have caused mechanical irritation of the adjacent bronchus during the patient's recent attack of diphtheria

2 The minor degree of accompanying anomalies and the presence of two of the three important secondary cardiovascular changes are consistent with the adult type of coarctation

3 This case is the third on record presenting the adult type of coarctation in an infant shortly after birth and therefore supporting the developmental theory of origin

4 The "adult" type of coarctation frequently and erroneously has been termed nondevelopmental It is a true abnormality of development arising in the descending limb of the primitive left aorta

## Book Reviews

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LEHRBUCH DER BLUTKRANKHEITEN FÜR ARZTE UND STUDIERENDE By PROF. DR. HANS HIRSCHFELD, Director of the Hematological Division of the University Institute for Cancer Research, Charité, Berlin, and Professor at the University of Berlin Price, Rm 22, bound Rm 24 Pp 263, with 48 illustrations Leipzig J. A. Barth, 1928

This is not a handbook for the specialist in hematology whose main interest is in the cytology of the blood. It is, as the title indicates, a textbook of diseases of the blood, intended primarily for the clinician and the medical student. As in the first edition of this book, clinical features and therapeutics are emphasized, while the discussion of blood pictures is restricted to what can be easily understood by those who have not had special training in morphologic hematology.

In some instances, this plan to limit the discussion of the cytology of the blood has led to the omission of some features which are important for differential diagnosis, for example, the spherical shape of the microcytes in hereditary hemolytic jaundice, the peculiar and characteristic neutrophil leukocyte of pernicious anemia, the character of the lymphocytes in benign lymphadenosis (infectious mononucleosis) and lymphatic reactions compared with those of acute lymphatic leukemia.

The general part of the book contains a brief but useful account of the common technical methods employed for the microscopic examination of the blood, including a description and illustration of the Hirschfeld precision pipets for accurately measuring the blood column and diluting fluid for cell counts. There are brief sections on the physicochemical and biologic properties of the blood, including the technic for determining blood groups. A section follows on the formation and destruction of blood, with a brief description of the histology of the blood-forming organs. The dualistic view of Naegeli is accepted as expressing the relationships of blood cells, with latent myeloid tissue in the spleen, in the form of oxydase-positive cells of the pulp and as adventitial cells in lymph nodes and liver, providing the mechanism for myeloid metaplasia of these organs in various pathologic states.

The section on the general pathology of the blood is one of the most interesting parts of the book. The general principles which govern the alteration of the blood are discussed, and the proper background is developed for the part dealing with diseases of the blood and blood-forming organs. It includes a discussion of the "shift to the left" in the leukocyte formula and a useful table presenting a grouping of diseases and pathologic states according to the type of leukocytosis which accompanies them.

More than half of the book is devoted to diseases of the blood and blood-forming organs, 41 pages being given to the anemias. Among the hemolytic anemias are included only those that show hemoglobinemia, such as various symptomatic types (black water fever, snake venom, saponin, etc.) and paroxysmal hemoglobinemia. Pernicious anemia, hemolytic jaundice and others which are frequently classified with the hemolytic anemias are excluded, because the destruction of erythrocytes takes place outside the blood stream. The other diseases are discussed under the following headings: hemoblastoses of the leukoblastic system (leukemia, chloroma) and of the erythroblastic apparatus (erythremia), genuine tumors of the hematopoietic system (lymphosarcoma, multiple myeloma, etc.), infectious granulating lymphomatoses (tuberculous, syphilitic, Hodgkins), diseases of the spleen, hemorrhagic diatheses and protozoan diseases of the blood. These chapters are followed by sections on general therapy of diseases of the blood, and secondary changes in the blood in diseases which are not primarily those of the blood. Finally there are a number of tables giving typical pictures of the blood illustrating the diagnostic and differential diagnostic importance of morphologic examinations of the blood.



In general, the more important diseases of the blood are discussed under the following headings: general clinical features, course, prognosis, pathologic anatomy, pathogenesis, differential diagnosis and therapy. The arrangement of the subject matter is logical and convenient for ready reference. Only well established facts are presented. There is an almost complete omission of controversial material and discussion of the literature. In spite of these intentional omissions this revised edition, with its modern point of view, should meet the requirements of those who wish to use it in medical practice, but who do not care to specialize in diseases of the blood. The revision shows many additions in both text and illustrations corresponding to the rapid advance which has been made in this field.

**LABORATORY DIAGNOSIS AND EXPERIMENTAL METHODS IN TUBERCULOSIS**  
HENRY STUART WILLIS, the Johns Hopkins University and Hospital, with a Chapter on Tuberculo-complement Fixation, by J. Stanley Wooley, Loomis Sanitarium. Price, cloth, \$3.50, keratol, \$4.25. Pp. 330, with illustrations and references. Springfield, Ill. Charles C. Thomas, 1928.

In this book, according to the preface, an attempt is made to describe the more important methods of laboratory diagnosis of tuberculosis and to consider some of the more significant procedures and principles involved in the experimental study of the disease.

The organization of the book is strikingly good and makes the work an invaluable and most accessible aid to the laboratory worker. Part 1 deals with general considerations of the fluids and excreta of the body. In part 2 the various bacteriologic methods of diagnosis are concisely and clearly described. The following sections give the methods of diagnosis by tuberculin and by serologic methods. Lastly, there are descriptions of methods for producing and studying the disease in animals and discussions of the technic of tissue culture and histologic technic for handling tissues. At the end of the book there is even a list of the equipment needed for a tuberculosis laboratory, with prices.

Dr. Willis' keen insight into the difficult details confronting the unaccustomed laboratory worker especially is clearly evident from the careful description of technic. Although the book is intended rather as a description of methods than as a discussion of theories, there is a great deal of valuable and often inaccessible theoretical information. References to an extensive bibliography lead the research worker to original sources. Data concerning the disinfecting capacities of varying degrees of heat and various concentrations of chemicals on the tubercle bacillus are especially commendable. The descriptions of the vital staining technic for studying the blood and tissues, of tissue culture methods and of the histologic technic for handling tissues are also valuable.

Dr. Allen Krause gives the following good description of the manual in his introduction: "The book will have been worth while if it succeeds in teaching that the laboratory diagnosis of the ordinary cases of tuberculosis can be accomplished by simple methods in an ordinary physician's hands in an ordinary physician's office."

**CRITERIA FOR THE CLASSIFICATION AND DIAGNOSIS OF HEART DISEASE** JOSEPH H. BANTON, M.D., W. C. MUNLY, M.D., M.C., U.S.A., ROBERT L. LEVY, M.D., and HAROLD E. B. PARDEE, M.D. (Chairman), a Committee Appointed by the Heart Committee of the New York Tuberculosis and Health Association. Arranged in conformity with the nomenclature for cardiac diagnosis approved by the American Heart Association. Price, \$1.50. Pp. 92. New York. Paul B. Hoeber, 1928.

The effective study of a chronic disease such as heart disease necessitates the accumulation of clinical data in many places over long periods of time. This cannot be accomplished satisfactorily unless a uniform nomenclature is adopted.

by the clinics encouraging such a study. The importance of precise labeling should be self-evident, and precision and uniformity in labeling depend on the accurate understanding of the labels.

This little book defines with remarkable clarity the criteria for the diagnosis and classification of pathologic conditions of the heart. The diagnostic nomenclature is that adopted by the American Heart Association. It was originally prepared and adopted by the Committee on Cardiac Clinics of the New York Heart Association and was introduced, in 1923, into the various clinics of that organization which is now the Heart Committee of the New York Tuberculosis and Health Association. In the opinion of the reviewer it should prove satisfactory in any clinic.

The major portion of the book is devoted to a discussion of the criteria for cardiac diagnosis. The belief is expressed that a comprehensive diagnosis should consist of four parts: etiologic, anatomic, physiologic and functional, that is to say, it should not only describe the structural changes in the heart but give the causes of such changes, indicating the type of disturbance of physiologic function, and defining the functional capacity of the heart. The descriptions and definitions are given concisely and clearly.

The committee has done a genuine service to the medical profession in the publication of this valuable book.

**THE OPIUM PROBLEM** CHARLES E. TERRY and MILDRED PILBINS. For the Committee on Drug Addictions in Collaboration with the Bureau of Social Hygiene. Cloth. Gratis. Pp. 1,042, with illustrations. New York: Committee on Drug Addictions, 1928.

This work is unique in its composition. It is a literary production in that it presents the problem of opium in its historic, physiologic, pathologic and forensic phases, purely from the standpoint of citation. The authors have quoted or summarized the essential features of approximately 400 references, consequently making this essentially a source book. In general, they have refrained from presenting their own conclusions; instead, they present the interpretations of the problem made by the different writers. This work is valuable to the student of almost any phase of the morphine problem, whether from the strictly scientific or the legal standpoint.

**THE DUODENUM. MEDICAL, RADIOLOGIC AND SURGICAL STUDIES** PIERRE DUVAL, JEAN CHARLES RAU and HENRI BECLERE, Surgical Clinic, Faculty of Medicine, Paris. Translated by E. P. Quam, M.D. Price, \$5. Pp. 205. St. Louis: C. V. Mosby Company, 1928.

The first half of this monograph is devoted to a discussion of the etiology, symptoms, diagnosis and treatment of periduodenitis. Beginning with cases of disease of the gallbladder in which the duodenum is involved by contiguity, the authors proceed to differentiate the symptoms due to disease of the gallbladder *per se* and those due to periduodenitis *per se*. The evidence submitted is entirely inadequate to justify the conclusions drawn. The same criticism applies to the chapter on essential and stenosing periduodenitis. Taken as a whole, facts submitted, including those of serial roentgenograms and operative controls, do not justify the attitude taken.

The chapter on chronic compression of the third portion of the duodenum seems a little more reasonable. Here, too, the authors seem unable to keep their enthusiasm under control. It is difficult for one who is unversed in "right-sided constipation and cecocolonic stercoral stasis" to conceive of a colonic type of duodenal stenosis.

The chapter on the radiologic signs of ulcer of the duodenal bulb is a well written, concrete presentation of fact. It is the really good part of the book. There is a similarly concrete discussion of intoxication in experimental intestinal obstruction. The clinical application of this condition in incomplete duodenal stenosis is not so obvious as it seems to have been to the authors.

CLINICAL MEDICINE OSCAR W. RETHEA, M.D., PH.D., Professor of Therapeutics, Tulane Graduate School of Medicine, and Professor of Clinical Therapeutics, Tulane School of Medicine. Cloth. Price, \$7.50. Pp. 700. Philadelphia: W. B. Saunders Company, 1928.

In the preface the author states that he has endeavored constantly to keep in mind that the great majority of patients must be treated in homes and under conditions which offer limited aid to the physician. The book concerns chiefly the diagnosis and treatment of about 100 of the most common diseases coming within the province of internal medicine. It is what it claims to be: a practical discussion of ordinary diagnosis and treatment, in which etiology and pathology receive little consideration. It will probably be welcomed by many practitioners.

## COLDS, AND ASTHMA ASSOCIATED WITH COLDS

### PREVENTIVE TREATMENT WITH VACCINES \*

I CHANDLER WALKER, M D

BOSTON

In a recent paper, Adkinson and I<sup>1</sup> reported the results of the bacteriologic examination of the sputum of a large number of asthmatic patients, for a period of years, with special reference to the streptococcus involved. In the present paper I wish to report the clinical application of these results. Patients who were subject to colds and to asthma associated only with colds were treated with vaccines comprising the prevalent streptococci for certain periods, as determined in the earlier investigation.

During the early studies on asthma, in 1916 and 1917, numerous patients were encountered who were nonsensitive and whose asthma, which seemed to be caused by bronchial infection, was associated, however, with little if any expectoration. It was desired to treat these patients with vaccines. Sputum was not available, however, and there was no information as to the bacteria to be used. Furthermore, many patients had sporadic attacks of asthma, and others had asthmatic attacks associated only with colds. Between attacks expectoration was not available. In the patients who had intermittent attacks of asthma with periods of freedom the attacks were attributed to various kinds of bacteria which were not constant for every cold or attack, as probably would be the case in patients with continuous asthma.

As an experiment, all good autogenous streptococcic vaccines were pooled for a period of a year, and all the asthmatic patients from whom sputum was not obtainable were treated with this pooled streptococcic vaccine, with beneficial results. This led to the treatment of patients with spasmodic asthma and colds with the pooled vaccine. Beneficial results often were obtained in these cases. In fact, the results were so encouraging that a more careful study and identification of the bacteria encountered in the sputum of asthmatic patients was begun. Since 1918, this study has been continued; the observations were recently reported<sup>1</sup>.

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\* Submitted for publication, Oct 23 1928

\* The laboratory work of this paper was done in the Medical Clinic of the Peter Bent Brigham Hospital Boston, in association with June Adkinson.

\* All the patients were seen and treated in private practice.

1 Walker, I Chandler, and Adkinson June Bacteriologic Examination of Seven Hundred and Twenty-Four Sputum from as Many Patients with Bronchial Asthma, Arch Int Med 41 601 (April) 1928

A brief summary of these observations follows. In the sputum of asthmatic patients, the prevalence not only of hemolytic and non-hemolytic streptococci, but of subgroups or individual varieties of both the hemolytic and nonhemolytic streptococci, varied from year to year. The changes in prevalence seemed to occur during the warm season of the year, the data were constant during the successive cool seasons of each year—fall, winter and spring. Not more than four of the eight hemolytic varieties of streptococci were prominent during any one period, among the eight nonhemolytic varieties not more than five predominated during any one period.

In 1919, the pooled autogenous vaccine previously mentioned was replaced by a mixed streptococcus vaccine which consisted of equal parts of the predominating streptococci for that period. As soon as new strains of the various individual types were isolated, they were added to the mixture, so that the ultimate vaccine consisted of many strains of each of the predominating streptococci for that period. The present paper deals with the clinical application of the laboratory observations already published.

The technic used in isolating and determining the varieties of the streptococci is described in an earlier paper. As by the time the individual variety had been classified the organism usually refused to grow, it was necessary to grow it in large quantities at the time it was inoculated into the serum waters. Even at this stage many cultures refused to grow. Thus a great deal more work was done than is evidenced by this paper. For each variety of streptococcus there was a container so labeled. After the various types were identified, washed in a physiologic solution of sodium chloride and concentrated and killed by heat, they were transferred to their respective containers or stock bottles. Since this procedure was carried on throughout the year, each type of bottle contained numerous strains of the same variety. From these concentrated stock varieties, dilutions of equal strengths of the various types of streptococci were made and pooled, thus the final mixed streptococcus vaccine consisted of equal strengths of the predominating streptococci. The count was approximately one hundred million organisms per minim, or fifteen hundred million per cubic centimeter.

The method of treatment consisted of weekly subcutaneous injections beginning with 3 minims, the equivalent of three hundred million organisms. The dose was increased by 1 minim weekly for a period of from eight to ten weeks. If a given dose caused much local or any general reaction, it was repeated before the amount was increased. Marked local reactions, or a general reaction were not common, but occurred in certain persons. For infants and young children the vaccine was diluted to one-half strength. Treatment was usually given during the fall and early winter for the following two reasons. 1. Most

patients are comparatively well during the summer, but during the fall, winter and spring, they are subject to colds and bronchial infections. During the fall, the prevailing types of streptococci are determined, these types seem to be constant throughout the succeeding cold period of the year.

Although patients with chronic bronchitis and asthma have been treated with this mixed streptococcus vaccine with considerable success, autogenous vaccines are preferable because the patients harbor certain organisms to which their resistance is low. In this group of cases, the sputum should be the best guide as to the organisms that cause bronchitis and asthmatic bronchitis. This paper, therefore, deals only with non-sensitive patients who had spasmodic or intermittent attacks of asthma separated by periods of freedom and those who had asthma associated only with colds, and persons susceptible to colds, though otherwise normal. The tables include the results for only the patients who were accustomed to having four or more asthmatic attacks or colds a year, since in such cases it was not difficult to estimate results. In the discussion of the results, some cases not mentioned in the tables are included in which some question may arise as to how definite the results from the vaccine were. In other words the figures presented in the tables represent cleancut definite results from which statistics may be made safely, but in the discussion of these results, cases are mentioned in which the benefit received from treatment with vaccine might be considered as problematic. Furthermore, only those cases are presented in which the patients were under observation for a period of four or more years.

Table 1 is reproduced from an earlier paper<sup>1</sup> in order to show the prevalence and frequency of the various types of streptococci during the period of this study. The constituents of the mixed streptococcus vaccine which was used each year were determined by the prevalence of the types as shown for that year in table 1.

During the fall, winter and spring of the period from 1920 to 1921 (table 1), the following most prevalent types of streptococci were incorporated into the mixed streptococcus vaccine: *Hemolyticus anginosus*, *infrequens* and *pyogenes*, and *Nonhemolyticus salivarius*, *fecalis* and *mitis*. For the period from 1921 to 1922, the following varieties of streptococci were used: *Hemolyticus subacidus*, *anginosus*, *infrequens* and *pyogenes*, and *Nonhemolyticus ignavus*, *salivarius*, *fecalis* and *mitis*. During the period from 1922 to 1923, the vaccine consisted of *Hemolyticus anginosus*, *infrequens* and *pyogenes*, and *Nonhemolyticus fecalis* and *mitis*. From 1923 to 1924, only *anginosus* and *pyogenes* of the hemolytic group were used, but of the nonhemolytic group, *ignavus*, *salivarius*, *fecalis* and *nonhemolyticus* type 1 were encountered with sufficient frequency. From 1924 to 1925, the mixed streptococcus vaccine consisted of *Hemolyticus subacidus*, *anginosus*, *infrequens*, *pyo-*

*genes* and *hemolyticus* type 1, of the nonhemolytic types, *ignavus*, *salivarius*, *fecalis*, *mitis* and *nonhemolyticus* type 1. It is noted, therefore, that of the hemolytic types of streptococci, only *anginosus* and *pyogenes* were constant for all the periods observed, and of the nonhemolytic types only *fecalis* and *mitis*, during the next period, 1925 to 1926, only two of the foregoing four types were prevalent. These facts illustrate the importance of constantly studying the bacteriology of these conditions in order to take advantage of variations as they occur. Furthermore, the nonfeasibility of using the same stock vaccine indefinitely is demonstrated. In fact, the same stock vaccine is not indicated for any two succeeding years but should be determined each

TABLE 1—*Prevalence and Frequency of Hemolytic and Nonhemolytic Streptococci and of Other Organisms*

Number of	1918 1919	1919 1920	1920 1921	1921- 1922	1922 1923	1923 1924	1924 1925	1925- 1926	1926 1927
Sputums examined	65	65	56	80	65	101	93	95	104
Hemolytic varieties recovered	51	46	49	70	68	21	54	42	110
Hemolytic varieties predominated	35	16	4	6	5	2	8	6	21
Hemolytic varieties alone	1	1	27	12	43	6	5	7	14
Nonhemolytic varieties recovered	54	51	24	62	26	108	115	93	115
Nonhemolytic varieties predominated	24	28	2	3	1	2	7	5	30
Nonhemolytic varieties alone	1	13	19	14	11	82	48	35	31
Hemolyticus subacidus recovered	17	19	0	8	2	2	8	13	42
Hemolyticus anginosus recovered	13	16	11	29	5	9	18	5	17
Hemolyticus infrequens recovered	8	3	16	12	28	2	10	11	14
Hemolyticus pyogenes recovered	10	7	20	14	26	6	10	4	7
Hemolyticus equinus recovered	1	0	1	2	2	0	2	0	7
Hemolyticus type 1 recovered	2	1	1	4	4	1	5	6	20
Hemolyticus type 2 recovered	0	0	0	0	1	0	1	1	1
Hemolyticus type 3 recovered	0	0	0	1	0	1	0	2	3
Nonhemolyticus ignavus recovered	16	20	0	5	0	13	12	28	45
Nonhemolyticus salivarius recovered	15	19	5	13	2	18	34	9	18
Nonhemolyticus fecalis recovered	3	5	10	19	9	28	25	29	14
Nonhemolyticus mitis recovered	14	7	8	17	10	25	17	4	10
Nonhemolyticus equinus recovered	0	0	0	1	0	6	4	4	5
Nonhemolyticus type 1 recovered	6	2	1	4	5	12	16	16	17
Nonhemolyticus type 2 recovered	0	0	0	0	0	4	1	1	3
Nonhemolyticus type 3 recovered	0	0	0	3	0	1	6	2	3
Strains of staphylococci recovered	8	16	1	5	5	16	8	4	4
Strains of bacilli recovered	6	8	5	7	8	1	10	6	10
Strains of other organisms recovered	5	5	3	0	2	0	0	0	3

fall and used only during the succeeding cool period of the same year.

As already noted, during the period from 1920 to 1921, six varieties of streptococci were used in the vaccine, and these represented all but 4 per cent of the streptococci that were recovered. During the next period, the eight varieties that were used in the vaccine represented all but 11 per cent of those recovered, during the remaining periods the vaccine consisted, respectively, of all but 16, 13 and 11 per cent of the types that were recovered. If it is evident, then, that after the use of the mixed streptococcus vaccine the frequency of colds and of asthmatic attacks associated with colds was greatly reduced for any one year, it must be equally evident that during that same year some of the colds and asthmatic attacks were apt to be due to varieties of streptococci which were not present in the vaccine but appeared more or less in the sputum of the patients.

Some of the patients who reported freedom from colds were not entirely free from them. Occasionally a patient would have all of the symptoms of a cold for a few hours. He might retire at night with all the symptoms of a severe cold but by morning all or practically all the symptoms would be gone. Naturally the ever present streptococcus

TABLE 2—Results in Thirty-Nine Patients, Susceptible to Colds and Asthma, Treated with Mixed Streptococcus Vaccine \*

1	O	C	1921	1c	6	1922	1c	12	1924	3c	18	1925	1c	18	1926	1c	12	1927	no tr
2	—	C	1921	W	12	1922	W	12	1923	N	24	1925	N	12	1926	N	12	1927	W 12
3	—	C	1921	W	22	1923	W	24	1925	1c	13	1926	W	12	1927	1c	12		
4	—	A	1921	N	4	1921	N	5	1922	2c	18	1923	N	14	1925	N	23	1926	W 18
5	—	O	1922	N	14	1923	W	10	1924	W	13	1925	W	11	1926	W	12	1927	W 12
6	—	C	1922	2c	16	1923	W	14	1925	W	11	1926	W	12	1927	W	18		
7	—	C	1922	1c	24	1924	W	12	1925	W	12	1926	W	12	1927	W	12		
8	—	A	1922	PF	7	1923	W	12	1924	W	12	1925	1c	12	1926	N	12	1927	N 12
9	—	C	1923	N	11	1924	W	15	1925	W	12	1926	W	12	1927	W	12		
10	—	A	1924	N	9	1924	N	24	1925	N	12	1926	N	12	1927	N	12		
11	—	C	1923	W	12	1924	W	12	1925	W	12	1926	W	12	1927	W	12		
12	—	A	1923	W	12	1924	W	13	1925	N	16	1927	1c	12					
13	—	A	1923	W	12	1924	W	13	1925	N	19	1927	W	18					
14	—	A	1923	W	12	1924	W	12	1925	W	12	1926 and 1927, no treatment, bad colds							
15	—	A	1923	W	10	1924	W	12	1925	N	8	1926	1a	24					
16	—	A	1923	N	4	1923	W	5	1924	W	8	1925	PF	36					
17	—	A	1923	N	6	1924	N	10	1924	2c	10	1925	2c	4	1926	1c	18		
18	—	A	1923	W	6	1924	1c	12	1925	W	12	1926	1c	18					
19	—	A	1923	1c	10	1923	1c	10	1924	PF	24	1926	N	12					
20	—	A	1922	PF	36	1925	N	10	1926	1c	12	1927	N	14					
21	—	A	1923	N	10	1924	N	14	1925	N	24								
22	—	A	1923	1c	4	1924	N	9	1925	4c	36								
23	—	O	1923	1c	12	1924	W	12	1925	W	12	PF since							
24	—	O	1923	1c	12	1924	W	12	1925	W	12	PF since							
25	—	A	1922	N	5	1923	PF	22	1925	PF	30								
26	—	O	1923	W	12	1924	N	24	1926	1c	24								
27	—	O	1923	N	12	1924	N	12	1925	PF	24								
28	—	O	1923	N	16	1925	W	7	1925	1c	30								
29	—	A	1923	W	12	1924	W	12	1925	PF	30								
30	—	O	1922	W	12	1923	N	24	1925	W	12								
31	—	A	1922	W	12	1923	N	48	1927	W	12								
32	—	O	1923	N	24	1926	W	24	1928	W	12								
33	—	A	1922	N	9	1923	N	44	1927	W	12								
34	—	A	1920	3c	24	1922	N	60											
35	—	A	1920	N	8	1921	N	12	1927	W	12								
36	—	O	1921	W	24	PF since													
37	—	O	1921	NG															
38	—	O	1922	NG															
39	—	C	1922	NG															

\* The following explanation of symbols applies also to tables 3 and 4. C in column 2, indicates a child of less than 2 years of age, a blank indicates an adult. O in column 3, means that the patient is susceptible to colds only, A means that he has asthma associated only with colds. The year that treatment was given appears in column 4. Beginning with this column, the table is divided into groups of three columns, represent (1) year, (2) results and (3) period of time in months between courses of vaccine. W indicates that the patient considered himself well as far as colds or colds and asthma were concerned, N means that the patient was well until the next course of vaccine was given or for the number of months indicated in the column to the right, 1c means that the patient had one cold only during that interval, 1a means one attack of asthma, sc means a slight cold (if it occurred in an asthmatic patient, it did not cause asthma), PF means that the patient considered himself practically free from colds or asthma, as compared with the years previous to treatment.

cannot be prevented from invading the mucous membranes of the nose and throat of persons, if the resistance of the subject is sufficient, however, the invading organisms sooner or later will be destroyed. Should the patient have symptoms for only a few hours, he considers himself free from colds, should symptoms be moderately severe and continue for a day or two, he usually reports that he has a slight cold or is practically free from one.

Table 2 gives the data for a group of thirty-nine patients who were under observation for periods of from five to eight years. Eleven of



these had been treated with five or six courses of the mixed streptococcus vaccine, eight had been given four courses, fourteen had received three courses and the remainder had been given one or two courses. Treatment of these patients began in the years from 1920 to 1923, inclusive, and has continued ever since. Twelve patients were less than 12 years of age when treated, the remainder were adults. Nineteen of the patients were susceptible only to colds, the remaining twenty were susceptible to asthmatic attacks only when they had colds. In the discussion following the table, fifty-one other patients who were similarly treated during this period will be mentioned.

#### ADDITIONAL DATA FOR CASES IN TABLE 2

Patient 1, a child who was 7 years of age when first treated, had had colds in his head and running ears for two years. Following a course of the vaccine in 1921, he had one cold in six months. In 1922, he was given another course of the vaccine with the result that he had one cold in the succeeding twelve months. In 1924, 1925 and 1926, likewise, he was given courses of the vaccine, and he had, respectively, three colds in eighteen months, one cold in the next eighteen months, and one cold in the next twelve months. In 1927, he did not receive the usual course of vaccine, with the result that the patient had five colds during a period of twelve months. During treatment, therefore, this patient averaged one cold in six months during 1921 and 1924, one cold in twelve months during 1922 and 1926, and one cold in eighteen months during 1925. Previous to treatment he averaged many colds in twelve months. During the second twelve months following the last course of vaccine, he had five colds but they were not so severe as those preceding the treatment.

Patients 2 and 3, a girl aged 14 years and her aunt, were both subject to colds, as noted in table 2, both were free from colds while taking treatment. The fourth patient, a school teacher, aged 34, had been subject to asthma whenever she had a cold, for sixteen years. As a result of treatment with vaccine in 1921, the patient was free from colds for two periods of only four and five months, respectively, following treatment in 1922, she had two colds in eighteen months, following treatment in 1923 and 1925, fourteen and twenty-three months, respectively, ensued before colds and asthma returned, the patient has been free from colds since a treatment in 1926.

Patients 5, 6, 7 and 8, all of whom began treatment in 1922, are so similar to the previous group of four patients just discussed that comment is not necessary except to remark that the results were much better. Eight other patients were similarly treated for a period of five years or more with equally good results. Since treatment was complicated, however, by either an autogenous vaccine or some protein sensitization, it is not fair to credit all benefit to the mixed streptococcus vaccine, the data for these eight patients, therefore, are not included in the table.

In patients 9, 10 and 11, who were given five successive courses of the vaccine, beginning in 1923, the results were similar, there was an average period of twelve months or more of freedom from colds and asthma following each course of vaccine. Patients 12 and 13, two children, a brother and sister, did exceedingly well following each of four courses of vaccine. Their ages were 4 and 6 years, respectively, both had been subject to colds and asthma since the age of 2 years. Patient 14, a child aged 5 years, had had a cold and asthmatic attack every

two weeks, on the average, since the age of 8 months. Excellent results followed treatment in 1923, 1924 and 1925. In 1926, the patient moved to California, and treatment was discontinued. Since then, she has had repeated colds in the head with asthmatic attacks. Patient 15, a boy, aged 13 years, averaged a cold and an asthmatic attack every month for nine years. Following treatment he was free for periods of ten, twelve and eight months, respectively, in the two years since the last course of vaccine he has had only one attack of asthma. Patient 16, a girl, aged 11 years, had her first attack of asthma at the age of 3 months, each year for the past five years she had had many attacks always following a cold. Removal of the tonsils and adenoids was of no benefit. The first course of vaccine, in 1923, was followed by a period of four months without the occurrence of a cold or asthma, following the second and third courses of vaccine, the patient was free from cold for five months and eight months, respectively, since the last course of vaccine in 1925, a period of three years, she has had an occasional cold but not one severe enough to cause her to seek more treatment, she has not had asthma.

Patients 17, 18, 19 and 20 gave similar results. All were adults who had had asthma associated with colds for periods ranging from ten to thirty years and averaging each year from four to as many as twelve colds and asthmatic attacks. Each succeeding course of vaccine was followed by a longer interval of freedom. In the case of patient 21, after each of three courses of vaccine, there were periods of ten, fourteen and twenty-four months, respectively, before he considered it necessary to take treatment. Patient 22, a woman, aged 31, had had repeated attacks of asthma for five years. During the four months following the first course of vaccine in 1923, she had one cold but no asthma, after the second course she was free from cold and asthma for nine months. After the third course in 1925, the patient went to St. John, New Brunswick, where she had lived before the first course of treatment. She has not had asthma as before, and during a period of three years she has had only three colds, none severe enough to cause her to seek more treatment.

Patients 23 and 24 were physicians who had had numerous colds in the head and congestion of two frontal sinuses for years. During the three years in which vaccine was given one cold only and no sinus trouble were reported. Since the omission of treatment in 1926, they have had only an occasional cold which has not been severe. In patients 25, 26, 27, 28 and 29, the results following vaccine treatment were similar. The average period of relief following the first two courses of vaccine was twelve months. Following the last course each patient had comparative relief for from two to two and one-half years. The first patient of this group, 25, was a boy, aged 13 years, who had had colds and asthma since the age of 3. In the fall of 1927, he became sensitized to ragweed pollen which caused asthma at that time, during the past spring he has been treated with the pollen. Patient 26 was a young woman who resided in Virginia and who wrote that "previous to the vaccine treatment I had cold after cold, but during the past six years while taking the three courses of vaccine I have had not more than three colds that amounted to anything." Patients 27 and 28 were children, aged 6 and 11 years, for two winters the former had had one cold after another in spite of removal of tonsils and adenoids, the latter also had frequent colds. Patient 29, a man, aged 51, had had repeated colds followed by a hard cough and asthma of two weeks' duration for three years previous to treatment. He wrote that he has not been entirely free from colds but that they last only a few days and do not force him to sleep sitting up in a chair as before, he has not considered treatment necessary during the last thirty months.

Patient 30, a student, did well following the three courses of vaccine but has not been heard from for the past two years. Patients 31, 32, 33 and 34 may be considered together, since the results which followed treatment are similar. The first patient of this group, 31, was a woman, aged 23, who lived in Tennessee. She had had asthma associated with colds since childhood, four months spent in Canada was the longest interval of freedom. Following the first course of vaccine, she was well for one year, and following the second course, for four years. Patient 32 was a girl, aged 12, who was subject to colds, cough and asthma for years with the exception of intervals which were spent in Cuba. Patient 33 was a child, aged 6 years, who had a cold, cough and asthma every three or four weeks for three years. Following the first course of vaccine in 1922, the patient was well for nine months. Then a second course was given, and she was well for nearly four years when she again began to take cold easily and had two attacks of asthma. Patient 34, a school teacher, following the first course of vaccine in 1920, had three colds in two years but no asthma, after the second course of vaccine she did not have colds or asthma for five years.

Patient 35 did well following two courses of vaccine. Then, like patient 25, he became sensitized to ragweed pollen for which treatment was given for two years. After the two seasons of ragweed treatment he reacted negatively to the pollen. No treatment, therefore, was given, and the patient remained free from colds and asthma until the winter of 1927, when colds and asthma returned and another course of the vaccine was given. The following four patients, although not clearcut enough in symptoms to present in the table, are somewhat similar to the last patient. A man who was sensitive to timothy pollen was given treatment with both the pollen and the vaccine with beneficial results. A boy who was sensitive to the hair of cats was given the vaccine with good results. Two patients were given one or two courses of an autogenous vaccine during the several years that they received the mixed streptococcus vaccine. These five patients, therefore, illustrate the importance of doing sensitization tests on patients who have asthma that is associated with colds. They also call attention to the advisability of using an autogenous vaccine whenever the patient has had a long protracted cold or attack of asthma. After the patient has become free from symptoms, whether from a sensitization or a bacterial infection, it is advisable to resume the mixed streptococcus vaccine. Further freedom from symptoms, however, after the use of this vaccine may be only assumed, for that reason the data for these patients are not presented in the table.

Patient 36, who had been susceptible to colds for years was free from colds for two years after a course of the vaccine. He then had an operation on his nose. During the succeeding four years he was comparatively free from colds. This patient is presented because he illustrates a group of twelve, three of whom were more or less susceptible to colds only, and nine of whom had more or less frequent attacks of asthma, associated with colds in the following way. After one series of vaccine treatments the patients were free from colds and asthma for a period of from nine to twelve months. Then they would have another cold or asthmatic attack. A second course of the vaccine would be followed by either complete or comparatively complete freedom from colds or asthma for a period of from three to five years. Since some of these patients had had only one cold or asthmatic attack a year, others had not had more than two such attacks a year and the remainder had had attacks at irregular intervals of time, treatment with vaccine cannot be given entire credit for the long periods of relief, however, most of the patients do give credit to the vaccine.

Patients 37, 38 and 39 were the only ones in whom treatment failed among the group of patients treated during the years from 1920 to 1923, inclusive. All three

had frequent and repeated head colds, patient 37 was a girl aged 11 years, patient 38 a woman and patient 39 a man. A second course of vaccine was not tried.

During the same period twenty-seven other patients, fifteen of whom were subject to colds only and twelve to colds and asthma, were treated for two successive years with results similar to those already mentioned. Since it has been impossible to follow many of these cases and learn the ultimate results, they are not mentioned in the table. They do, however, substantiate the claim of immediate beneficial results from the use of the mixed streptococcus vaccine.

In table 3 are presented results for the patients who were first treated in 1924, and who have been under treatment ever since, a period of four

TABLE 3—*Results in Twenty-Eight Patients, Treated with Streptococcus Vaccine for Four Years, Beginning with 1924*

1	C	A	1924	N	4	1924	N	8	1925	W	6	1925	N	10	1926	N	12	1927	2c	12
2	—	A	1924	N	5	1924	PF	6	1925	PF	7	1926	PF	8	1926	PF	10	1927	PF	12
3	—	A	1924	N	6	1925	N	6	1925	W	6	1926	W	6	1926	W	6	1927	W	6
4	C	A	1924	2c	12	1925	N	9	1926	N	5	1926	N	9	1927	N	8			
5	—	A	1924	PF	6	1925	PF	8	1926	N	12	1927	1a	18						
6	—	A	1924	W	7	1925	W	6	1926	W	7	1926	PF	24						
7	C	A	1924	W	12	1925	sc	12	1926	W	12	1927	W	12						
8	—	C	1924	PF	12	1925	W	12	1926	W	20									
9	—	A	1924	W	12	1925	no tr		1926	1c	12	1927	1c	12						
10	—	O	1924	N	12	1925	N	12	1926	N	12	1927	W	12						
11	—	A	1924	N	11	1924	N	12	1926	N	12	1927	W	12						
12	O	A	1924	N	12	1925	W	12	1926	W	12	1927	no treatment							
13	—	C	1924	W	9	1925	W	12	1926	W	6									
14	C	O	1924	N	14	1925	N	17	1926	W	12	1927	W	12						
15	—	O	1924	W	12	1925	sc	12	1926	N	12	1927	W	12						
16	—	O	1924	W	12	1925	W	12	1926	W	12	1927	1c	12						
17	—	O	1924	W	12	1925	W	12	1926	W	12	1927	sc	12						
18	C	O	1924	PF	12	1925	W	12	1926	W	12	1927	no treatment							
19	C	O	1924	W	12	1925	W	12	1926	PF	12	1927	no treatment							
20	C	A	1924	N	15	1925	W	12	1927	W	12									
21	O	A	1924	N	11	1925	W	12	1926	no tr		1927	better							
22	—	A	1924	N	16	1925	N	19	1927	W	12									
23	—	C	1924	W	12	1925	N	24	1927	W	12									
24	O	A	1924	N	7	1924	N	36	1927	W	12									
25	O	A	1924	PF	10	1925	W	12	1926	PF	15									
26	O	A	1924	W	24	PF since														
27	C	C	1924	W	24	PF since														
28	—	O	1924	NG																

years. Thirteen of these were children, and twelve of the patients were susceptible only to colds. Eighteen other patients are mentioned in the discussion.

#### ADDITIONAL DATA FOR CASES IN TABLE 3

The results for the first four patients are similar in that any benefit derived from treatment seemed to last for only a few months, making it necessary to give two courses of vaccine each year. Patients 1 and 4, children, aged 4 and 3 years, respectively, were both susceptible to colds and were rarely free from asthmatic attacks for more than a week at a time. The former lived in Kansas and was not benefited while in Florida or Texas. Patient 2 was an adult who lived in Georgia and had had frequent colds, for nine years he had not been free from asthma for more than two weeks at a time. During treatment he did not have severe attacks of asthma or severe colds. He now considers himself practically free from colds, about twice a year when he has a mild cold that causes asthma he sends for more vaccine. Patient 3 who takes a course of the vaccine every six months has been free from asthma and colds.

Patients 5 and 6 were adults. The former who had had colds and asthma for six years, had little trouble for six and eight months, respectively, following the first two courses of vaccine, and for a year following the third and fourth courses of vaccine. The latter patient voluntarily took courses of vaccine at short intervals and now considers himself completely cured. Patient 7, a child of 8 years, had a cold and asthmatic attack on an average of every three weeks for four years, he lived in North Carolina. Patient 8 was an adult who was susceptible only to colds. Patient 9, who had had asthma, had no asthma and only two colds during the three years that he took treatment. During an intermediate year when he was not given treatment he had five colds that resulted in asthma. Patient 10 was a young woman who had been susceptible to colds. Patient 11 was a young man who had asthmatic attacks associated with colds.

Patient 12 was a girl, aged 7 years, who lived in New Brunswick and who was susceptible to colds that caused asthma. During the period following each of three courses of vaccine given during a year, the patient was free from colds and asthma. During the last year in which no treatment was given, the patient had an occasional cold and asthmatic attack. Patient 13 was interesting in that she was free from colds following treatment with vaccine while she was in this locality, but while in Glasgow, Scotland, she had bronchitis, laryngitis, influenza and colds. Patient 14, a boy, aged 8 years, was free from colds for a year or more following each course of the vaccine. Patients 15, 16 and 17 were women who were extremely susceptible to colds and who seemed to obtain satisfactory results from the vaccine.

Patients 18 and 19, who were brothers, aged 7 and 5 years, respectively, had five or six colds yearly. Following three successive courses of vaccine at yearly intervals, both of them were comparatively free from colds. During a second year without treatment each had only one cold that was at all troublesome. Patients 20 and 21 were children who had many colds that resulted in asthmatic attacks. The former, a boy, aged 4 years, had averaged a cold and asthmatic attack from every two to four weeks since he was 1 year of age. The latter, a boy aged 5, had had five colds and asthmatic attacks during the previous year. He omitted treatment in 1926, and had numerous colds with asthma, the next year he had treatment and was well following the treatment. Patients 22 and 23, adults, both of whom had had colds and asthma for eight years, were well for periods of from one to two years following courses of vaccine. Patients 24 and 25 were boys, aged 4 and 8 years, who averaged a cold and asthmatic attack every six or eight weeks during the previous two or more years. The first patient was free from colds and asthma following the first course of vaccine, following a second course he was practically free for three years, after which colds and asthma returned, after a third course of vaccine he was well for a year. The second patient obtained good results for periods of from ten to fifteen months following each course of vaccine.

Patients 26 and 27 were boys, aged 2 and 10 years, respectively. Since the age of 9 months, the former had had a cold with asthma every three or four months, the latter was subject only to colds. After one course of vaccine, neither patient had colds or asthma for two years, without treatment, both were practically free from colds during the subsequent two years. Three other patients, all adults, deserve mention in that following one course of vaccine in 1924, they were free from colds for periods of thirty, thirty-four and thirty-six months, respectively, all reported for treatment again in 1927, and so far have been well. In these three cases, however, the patients had not had a sufficient number of colds to justify their inclusion in the table. Eleven other patients, seven of whom were subject to frequent asthmatic colds and the other four to frequent colds, should be mentioned because each was treated with the vaccine for two successive years with results as good as those already reported, these cases however have not been followed

during the last two years. Four other adults, three of whom were subject to frequent colds and asthmatic attacks and one to colds only, all receiving only one or two courses of vaccine, report that the frequency, severity and duration of colds have been greatly reduced, so much so that they feel that further treatment is at present not needed. Patient 28 was the only one among the patients who began the treatment in 1924 in whose case the treatment failed.

In table 4 the results for thirty patients are presented who began treatment in 1925, and who were treated or under observation for the following three years. Twelve of this group were children, eleven were susceptible to colds only. In the discussion of table 4, twenty other cases are mentioned.

TABLE 4—*Results in Thirty Patients Treated with Streptococcus Vaccine for Three Years, Beginning with 1925*

1	O	A	1925	N	9	1926	PF	9	1927	1c	12
2	—	A	1925	W	5	1926	1a	11	1927	N	8
3	—	C	1925	N	8	1926	N	8	1926	N	9
4	—	A	1925	N	8	1926	N	9	1927	W	12
5	O	A	1925	N	9	1926	N	9	1927	1c	12
6	—	A	1925	PF	9	1926	PF	15	1927	W	11
7	O	A	1925	N	7	1926	N	17	1927	W	12
8	—	C	1925	W	9	1926	W	13	1927	W	12
9	—	A	1925	N	10	1926	W	12	1927	1c	12
10	C	A	1925	1c	12	1926	N	14	1927	1c	12
11	—	C	1925	N	11	1926	W	10	1927	W	13
12	O	A	1925	PF	12	1926	PF	17	1927	no tr	
13	C	A	1925	N	10	1926	W	12	1927	W	12
14	—	C	1925	W	12	1926	W	12	1927	W	12
15	—	C	1925	W	12	1926	W	12	1927	1c	12
16	C	O	1925	W	10	1926	W	12	1927	1c	12
17	—	C	1925	W	12	1926	W	12	1927	W	12
18	—	A	1925	W	12	1926	W	12	1927	W	12
19	C	A	1925	1c	12	1926	1c	12	1927	1c	12
20	C	A	1925	PF	12	1926	PF	12	1927	autog	
21	—	C	1925	W	12	1926	W	12	1927	1c	12
22	—	A	1925	N	11	1926	N	10	1927	W	12
23	C	A	1925	PF	12	1926	PF	12	1927	no tr	
24	C	C	1925	2c	12	1926	N	15	1927	W	12
25	C	A	1925	N	10	1926	W	24			
26	—	C	1925	N	24	1927	W	12			
27	—	A	1925	N	24	1927	W	12			
28	—	C	1925	W	36						
29	—	A	1925	PF	36						
30	—	C	1925	NG	36						

#### ADDITIONAL DATA FOR CASES IN TABLE 4

The first five patients may be described together. They are similar in that all had a recurrence of colds and requested treatment of eight or nine months after the previous course of vaccine. Patients 1 and 5 were children and the other three were adults, all, with the exception of patient 3, had asthma associated with colds for periods ranging from two to nineteen years. Patient 4, a boy, aged 4 years, began to have colds, bronchitis and asthma at the age of 1 month. Patient 3 had colds only with every change of the weather, which was rather variable in his locality. Patients 6, 7 and 8 obtained considerable benefit from the first course of vaccine, after each of the other two courses they were free from colds for a year or longer. Patient 6 was an adult who has had asthma associated with colds for twenty-four years. Patient 7, a boy, aged 8 years, had attacks of asthma with colds on an average of every four or five weeks for four years, following whooping cough. Patient 8 is an adult who was subject only to colds.

Patients 9 to 18, inclusive, may be grouped together. All were either comparatively or entirely free from colds during the three years in which they received

treatment Patient 10, a boy, aged 12 years, had had a cold with asthma every few weeks for years, patient 12, a boy, aged 4 years, had had colds and asthma for two years, during the year 1927, when treatment was omitted, he averaged a cold every two months, patient 13 was a girl, aged 7 years, who had had colds and asthma since she was 1 year of age, patient 16, a boy, aged 7 years, complained of having colds all of the time The remaining patients in this group were adults Patient 11 had had frequent colds and attacks of bronchitis for twenty years, patients 14, 15 and 17 had been extremely susceptible to colds for five years Patient 18, who had had asthma associated with colds for years, requests the vaccine each fall, even though free from symptoms

Patient 19, a boy,  $3\frac{1}{2}$  years of age, had had four colds and asthmatic attacks a year before treatment, after treatment for the last three years, he had had only one cold a year, which was not serious Patient 20, a boy, aged 6 years, had colds, bronchitis and asthmatic symptoms, following each of two courses of vaccine he was comparatively free from these conditions for a year When he presented himself for a third course of treatment, he was having such a prolonged attack of bronchitis that an autogenous vaccine was deemed advisable Patient 21, a man, aged 52, had had frequent colds as long as he could remember Patient 22, a woman, aged 62, had had asthma all her life, during each series of vaccine treatment the asthma would cease and would not return for a period of ten or more months Patient 23, a girl, aged 3 years, had had asthmatic attacks associated with colds for the last ten years, during the two years that she was treated she had only three slight attacks, further treatment, therefore, was not requested During the next year, however, when treatment was not given, the patient had croup, bronchial pneumonia and asthmatic colds Patient 24, a boy, aged 6 years, had a cold every two or three weeks for two or more years During the three years that he was given three courses of vaccine he had three slight colds

Patients 25, 26 and 27 were given only two courses of the vaccine Patient 25, a girl, aged 6 years, had had colds with wheezing spells and a severe cough since the age of 9 months After the first course of vaccine she was free from colds for ten months, and since the last vaccine was given two years before this article was written, she has been well Patient 26, a man, aged 52 years, was extremely susceptible to colds After the first course of vaccine he was free from colds for two years Then with the first cold he had another course of vaccine and has been free from colds since then Patient 27, a boy, aged 13 years, had had asthma with colds since the age of 2 years, following whooping cough After the first course of vaccine he did not have colds or asthma for two years, then he had two colds in one month and reported for treatment After the last course of vaccine he had not had colds or asthma

Patient 28, the mother of patient 27, was subject to frequent head colds, but these have not recurred after one course of vaccine Patient 29, a woman, had attacks of asthma associated with colds every few weeks for three years After one course of vaccine she has been so free from colds and asthma that she feels that another course of treatment is not necessary The results in eight other patients, five of whom are children, and three of whom were subject only to colds were similar to the last patient in that, following one course of vaccine, the patients have all been comparatively free from colds and asthma, further treatment, in fact, has not been requested Since their colds and asthmatic attacks were at more infrequent and irregular intervals in the past, data for these patients were not included in the table For the same reason, those for five other patients who had a course of vaccine for each of the last three years with good results were not included in

the table Seven other patients were treated with equally good results for two successive years but were not followed up The only failure in the series of patients treated in 1925 occurred in patient 30, an adult who was extremely susceptible to colds in the head

#### COMMENT

A total of 312 courses of vaccine were given to the 97 patients concerning whom data are recorded in the tables In 22 instances there was freedom from colds and from asthma associated with colds for six months or less, in 28 instances for from seven to nine months, inclusive, in 124 instances, for from ten to twelve months, inclusive, and in 20 instances for from thirteen to eighteen months In 13 instances, patients were free from colds for two years after one course of vaccine, 5 patients were free from colds for three or more years In other words, in 67 instances, or 21 per cent of this group of patients, there was freedom for less than one year from colds or colds that caused asthma, one third of these patients were free from these conditions for ten or eleven months In 111 instances, or 36 per cent, there was freedom from colds for one year, in 42 instances, or 13 per cent, for more than one year,

There are two reasons why such a large number, namely, 111 patients, took the treatment again at the end of a year One reason is that, as already stated, the new constituents of the vaccine or the prevailing types of streptococci are determined every fall, and until sufficient time has elapsed to justify the composition of the vaccine not many patients are given the treatment Consequently, each year many more patients are started on the treatment during October and November than at any other time, since patients are advised to begin the vaccine treatment at that time, a large number of patients take the vaccine every fall whether they need it or not The second reason is that each fall the prevailing types of streptococci are somewhat different from those of the preceding fall, colds are being caused by these new or different varieties with which treatment either has never been given or not for at least two years The second reason applies also to many instances when a cold occurred within a year after the vaccine treatment Many of these patients began the use of vaccine in the middle of the winter or even in the spring of the first year of treatment Consequently they were protected only until the succeeding fall when a different type of vaccine was indicated

Because of the two foregoing reasons, it is difficult to judge the permanence of the beneficial effects of the vaccine The fact that of 111 patients who were free from colds or colds and asthma for a year, were still free from colds and did not need treatment at the end of the year, shows that if the vaccine is given in the fall, its beneficial effects lasts for a year in most instances The period of freedom from colds was



shorter in only 63 instances, and this was partly offset by the fact that 42 patients were free from colds for more than one year

Thirty-five of the 312 courses of vaccine resulted in practical freedom from colds or colds and asthma. Ten of these patients were practically free from colds for intervals of from six to ten months, 10 others, for a year, 15 for fifteen or more months, and 11 of these 15, for two or more years. The fact that there were as many instances in which benefit lasted for a year as for less than a year, and that one-half as many patients were benefited for more than a year, shows further that the beneficial effect of the vaccine lasts for a year, at least in a large percentage of the cases, when given in the fall.

In 38 of the 312 cases a cold or an attack of asthma with a cold occurred between two courses of vaccine. In 12 instances there was a cold during the interim of from four to eleven months, in 18 instances there was a cold during the interim of a year, and in 8 instances, one during an interim of from eighteen to twenty-four months. A cold occurred in a year, therefore, in one and one-half as many instances as in less than a year, in two-thirds as many instances, there was one cold in an interim of eighteen or more months. This is additional evidence that the vaccine should be expected to have a beneficial effect for a year if it is given in the fall.

The last two paragraphs contained a general discussion of the results of the vaccine treatment without any consideration of the individual patient. A general discussion of the patients and the results obtained follows.

In 43 of the cases presented in the tables the patients were susceptible only to colds. Eight of these patients were free from colds throughout the entire period of observation, lasting for from four to eight years, 10 patients had only one cold during this time, 1 had two colds, 1 had a cold following each of two courses of vaccine, 11 were free from colds for periods of a year or more before a cold developed which led them to report for more treatment, 3 were practically free from symptoms for a year, 2 had a return of colds in an interval of less than a year after treatment, 2 others had a cold every six or nine months and 5 were not benefited by the one course of vaccine they received. In other words, 44 per cent of the patients who were susceptible only to colds were free from colds for one year or more following each course of vaccine, 23 per cent of the remainder had only one cold during the several years in which they were under treatment, 11 per cent were failures and the remaining 22 per cent had considerable relief varying from practical freedom from colds for a year to freedom for periods of six months or more.

Ten of the 54 patients who had asthma associated only with colds were free from colds and asthma for one year or more following each course of vaccine, 7 others needed treatment at the end of a year,

3 patients had either one cold or one attack of asthma, and 3 others had either two colds or two attacks of asthma during the several years in which they were under treatment, 7 were practically free from colds and asthma for yearly periods, 9 were free for periods of from six to nine months before treatment was repeated, 4 who were free for a few months following one course of vaccine were free for two or more years following a second course, and the remaining patients showed results too diversified to classify

In other words, 39 per cent of the patients who suffered from repeated colds and asthma were free from these conditions for a year or more after each course of vaccine, another 24 per cent either were practically free or had only one or two colds during the period of treatment, 16 per cent required treatment at intervals of from six to nine months and the remaining 29 per cent received benefit for intervals which varied too much to classify

A summary of the 97 cases reveals that 37 per cent of the patients were free from colds for a year or more following each course of vaccine throughout the period of treatment which lasted from four to eight years, 13 per cent had only one cold during several years of treatment, another 13 per cent were practically free from colds, 11 per cent were relieved for periods of less than a year after each course of treatment, there were failures in 5 per cent, and the remaining 1 per cent were relieved for intervals varying from six months to two or more years following a course of vaccine. In other words, the treatment failed in 5 per cent of the patients, in another 11 per cent, although not failures, did not show so permanent a benefit as was desirable, in the remaining 84 per cent, however, there was freedom or comparative freedom from colds and from colds associated with asthma for periods of a year or more following each course of vaccine

Thirty-seven of the 97 patients presented in the tables were children, and 60 were adults. Twelve of the 37 children were susceptible to colds only. Ten of these were free for a year or more following each course of vaccine, the others needed treatment more often than once a year. The other 25 children were susceptible to colds that caused asthma, 14 of these were free from colds and asthma for a period of a year or more following each course of vaccine, 6 others either were practically free from colds or had only one cold or asthmatic attack during the several years of treatment, and the remaining 5 children were free from colds for less than a year following some of the courses of vaccine. Therefore, the children who were susceptible only to colds received much more benefit from the treatment than those who had asthma associated with colds, although all but one of the patients with asthma were greatly benefited.

Thirty-two of the 60 adults were susceptible only to colds, and the remaining 28 had asthma with colds. Nineteen of the 32 patients

who had colds only were free from them for periods of one year or more, 7 patients had one cold during the several years of treatment, in 2 patients, the interval between colds was less than one year, and in 4 patients the treatment failed. By the process of exclusion it is evident that, except for the 4 failures, the patients who were susceptible only to colds derived more lasting beneficial effects from the vaccine than did those who had asthma with colds.

Thus, the vaccine seemed to give the best results in children who were susceptible to colds only and the least benefit to adults who had asthma associated with colds. With children who had asthma with colds and with adults who were susceptible to colds only, the results were considerably better than those obtained in adult patients who had asthma with colds.

More of the patients lived in Massachusetts than in any other state, however, a sufficient number lived in Maine, New Hampshire, Rhode Island and Connecticut to justify the statement that the vaccine gave equally good results throughout the New England states. Two patients lived in Minnesota, two in New Brunswick and one each in Virginia, West Virginia, Tennessee, Georgia, North Carolina and Kansas, none of these patients was among the failures.

A few of the children who seemed to be protected from colds had measles, whooping cough, chickenpox and scarlet fever. This is evidence that the symptoms of a common cold which precede these diseases are early symptoms of the infectious disease itself rather than of a common cold which predisposes to the disease. This would seem to be true also of the few adults who had pneumonia and influenza.

#### SUMMARY AND CONCLUSIONS

The results secured when 97 patients who were subject to colds were treated with mixed streptococcus vaccine are discussed in detail. Previous to treatment 43 of the patients were subject to four or more colds a year, and 54 were subject to four or more attacks of asthma which were always associated with colds. The patients were treated periodically with a vaccine consisting of the most prevalent types of streptococci for each respective period. Thirty-nine patients were treated or were under observation for five or more years, 28 others, for four years, and 30 others, for three years.

Eighteen per cent of the patients were free from colds and asthma associated with colds, 12 per cent were practically free, 19 per cent had only one or two colds during the period of from three to five or more years that they were treated or under observation, and 10 per cent were free from colds for a year or more following each course of vaccine. Therefore, 59 per cent of the patients obtained either freedom or comparative freedom from colds and asthmatic colds for periods of a year or more following each course of vaccine.

Sixteen per cent of the patients required a course of vaccine oftener than once a year, their freedom from colds varied from six to eleven months after each course of treatment. In 20 per cent of the patients the results represented some combination of those already mentioned and were too complex to classify, for example, following the first course of vaccine the patient might be free from colds for months, following another, practically free for a year, and following a third, entirely free for a year or more. In 36 per cent of the patients, therefore, the results were satisfactory for periods of more or less than a year, and the frequency of colds was reduced by 50 or 75 per cent.

Five per cent of the cases in which the patients did not show any benefit following the course of vaccine are called failures.

Each year the vaccine consisted of those streptococci which represented between 85 and 90 per cent of the prevailing types. It is possible, then, that other varieties of streptococci, which were less prevalent and yet comprised from 10 to 15 per cent of those encountered, could cause colds in patients who were not entirely free from colds. A later paper will present evidence that this is the case, also that *Staphylococcus pyogenes-aureus* sometimes seems to be a cause of colds.

In addition to the 97 cases presented in the tables and discussed in detail, 89 other similar cases in which the patients were similarly treated, are mentioned in the discussion. Since it was not possible to follow up some of the patients for more than two or three years, and since the others were subject to colds at less frequent and more irregular intervals, it is difficult to determine the extent and duration of protection from colds. However, since as far as it was possible to follow these patients, the results, which were satisfactory and did not include any failures, substantiates those presented in detail.

Since the prevalence of the various types of streptococci varies from year to year, it is advisable constantly to study the sputum and the nasal secretions of patients with colds. It is essential to do so each fall in order to know the prevailing varieties of streptococci for the ensuing cold period of the year, in other words, the same combination of varieties of streptococci does not suffice for more than one year.

Each fall, in the New England states, the administration of a vaccine consisting of the varieties of streptococci that are most prevalent at that time seems to reduce greatly the susceptibility to colds during the fall, winter and spring.

It seems advisable to administer such a vaccine each fall. The varieties of streptococci vary in their prevalence from year to year, thus necessitating constant study and yearly changes in the composition of the vaccine.

# PANCREATIC FUNCTION

## IV THE HUMORONEURAL REGULATION OF THE GASTRIC, PANCREATIC AND BILIARY SECRETIONS <sup>†</sup>

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The regulatory mechanism of the secretion of the digestive juices was obscure until recently Naunyn<sup>1</sup> proved that puncture diabetes (Piqure diabetes) has an inhibitory influence on the secretion of bile. He attributed the inhibitory effect to the alteration of blood pressure in the liver. The classic experiments of Bayliss and Starling<sup>2</sup> showed, in a striking way, that the secretory glands of the pancreas can be excited to activity through influences that reach them by humoral, as well as by nervous channels. They showed that when dilute acid acts on the duodenal mucosa, a substance, secretin, is formed that can accelerate the flow of pancreatic juice even when all nervous connections with the secretory gland are severed. They reach the conclusion that such a mechanism is involved normally in the production of pancreatic secretion. Edkins<sup>3</sup> found that extracts of pyloric mucous membrane contain a substance that causes the secretion of a certain amount of gastric juice, if injected into the jugular vein. The normal gastric secretion is therefore due to the cooperation of two factors. The first and most important is a nervous stimulus determined through the vagus nerves by stimulation of the mucous membrane of the mouth or by the arousing of appetite in the higher centers of the brain. The second factor, which provides for the continued secretion of gastric juice long after the mental effects of a meal have disappeared, is a chemical process, depending on the production in the pyloric mucous membrane of a specific substance, or hormone, gastric secretin or gastrin that,

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\* A Preliminary Report was made by Okada, S., Kuramochi, K., and Tsukahara, T. The Humoro-Neural Regulation of the Gastric, Pancreatic and Biliary Secretions, Proc. Imperial Acad. Tokyo **4** 178 (April 12) 1928

1 Naunyn, B. Beitrage zur Lehre vom Diabetes Mellitus, Arch. f. exper. Path. u. Pharmacol. **3** 325, 1875

2 Bayliss, W. M., and Starling, E. H. The Mechanism of Pancreatic Secretion, J. Physiol. **28** 325, 1902

3 Edkins, J. S. The Chemical Mechanism of Gastric Secretion, J. Physiol. **34** 133, 1906

acting as a chemical messenger to all parts of the stomach, is absorbed into the blood and causes activity of the various secreting cells in the gastric glands Benedicenti<sup>4</sup> noticed that the secretion of pancreatic juice in a dog provided with a fistula was inhibited by injections of epinephrine hydrochloride, and Glaessner and Pick<sup>5</sup> proved later that this secretion is thoroughly stopped by the injection of a large dose of epinephrine hydrochloride The inhibitory influence of epinephrine or of suprarenal extracts on the pancreatic secretion was further demonstrated by Rogers and his associates<sup>6</sup> and by us<sup>7</sup> Rogers and his associates found that the noncoagulable part of watery extracts of liver, when injected subcutaneously into a dog, caused a rapid increase of pancreatic secretion, while injections of extracts of the thyroid and the thymus caused only a slight increase As to the influence of epinephrine on the secretion of bile, Langley<sup>8</sup> and Alpern<sup>9</sup> thought that it had an excitatory influence, but Ott and Scott,<sup>10</sup> Dawns and Eddy,<sup>11</sup> Neubauer,<sup>12</sup> Kusakabé,<sup>13</sup> Adachi<sup>14</sup> and Sakurai<sup>15</sup> observed that it caused, in general, a decrease of the secretion of bile The effect of epinephrine on the secretion of gastric juices has also been studied

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4 Benedicenti Gior d r Accad di med di Torino, 1906, cited by Glaessner and Pick (footnote 5)

5 Glaessner, K, and Pick, E P Untersuchungen uber die gegenseitige Beeinflussung von Pankreas and Nebennieren, *Ztschr f exper Path u Therap* **6** 313, 1909

6 Rogers, J, Rahe, J M, Fowcett, G G, and Hackett, G S The Effects of the Subcutaneous Injection of Organ Extracts upon the Flow of Pancreatic Secretion, *Am J Physiol* **40** 12, 1918

7 Okada, S, Sakurai, E, Imazu, T, and Kuramochi, K Studies on the Pancreatic Function, *Nippon Naika Gakkai Zasshi* **15** 381, 1927

8 Langley, J N Observations on the Physiological Action of Extracts of the Suprarenal Bodies, *J Physiol* **27** 237, 1901

9 Alpern, D Zur Frage der Wechselbeziehungen zwischen innerer und ausserer Sekretion II Ueber den Einfluss einiger Hormone und proteogener Amine auf die Gallenabsonderungsfähigkeit der Leber, *Biochem Ztschr* **137** 507, 1923

10 Ott, J, and Scott, J C The Action of Animal Extracts upon the Flow of Bile, *Proc Soc Exper Biol & Med* **13** 12, 1915

11 Dawns, W A, and Eddy, N B The Influence of Internal Secretions on the Formation of Bile, *Am J Physiol* **48** 192, 1919

12 Neubauer, E Beitrage zur Kenntnis der Gallensekretion I, *Biochem Ztschr* **109** 82, 1920

13 Kusakabé, S The Influence of Thyroid Extract on the Secretion of Bile, *Nippon Naika Gakkai Zasshi* **10** 484, 1922

14 Adachi, A Beobachtungen uber die Wirkung von Acetylcholin, Pilocarpin, Atropin, Kaliumchlorid, Adrenalin, Calciumchlorid und Nicotin auf die Gallenausscheidung am Gallenblasenfistel-Hunde, *Biochem Ztschr* **140** 185, 1923

15 Sakurai, E Experimentelle Untersuchungen uber den Einfluss von Insulin, etc, auf die Gallensekretion, *Proc Imperial Acad* **2** 185, 1926

Yukawa<sup>16</sup> found that the intravenous or oral administration of epinephrine in small doses caused an increase of gastric secretion in a dog with a small stomach of Pavlov. An excitatory influence was also reported by Loeper and Verpy,<sup>17</sup> Lim,<sup>18</sup> Ivy and McIlvyn<sup>19</sup> and Ivy and Javois<sup>20</sup> with use of various methods of administration. On the other hand, Hess and Gundlach,<sup>21</sup> Rothlin<sup>22</sup> and Fusé<sup>23</sup> found a remarkable inhibition of the secretion on administration of epinephrine. Sirotinin,<sup>24</sup> using Heidenhain's isolated small stomach to exclude all the inhibitory influence, found, with and without feeding, on subcutaneous injection of epinephrine, an increase of from one and a half to two times the normal amount of secretion. After the discovery of insulin, there arose a new theory as to the action of this hormone on the secretion of the digestive juices. Collazo and Dobreff<sup>25</sup> found that insulin had an excitatory influence on the pancreatic secretion. This was confirmed by Ono,<sup>26</sup> by Yoshida,<sup>27</sup> by Arima,<sup>28</sup> by us<sup>29</sup> and by others, though Lambert and

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16 Yukawa, G. Klinisch-experimentelle Untersuchungen der Adrenalinwirkung auf die Magendrüsen, *Arch f Verdauungskr* **14** 166, 1908

17 Loeper and Verpy. L'adrenaline sur le tractus digestif, *Compt rend Soc de biol* **80** 703, 1917

18 Lim, R. K. S. The Question of Gastric Hormone, *Quart J Exper. Physiol* **13** 79, 1922

19 Ivy, A. C., and McIlvyn, G. B. The Excitation of Gastric Secretion by Application of Substances to the Duodenal and Jejunal Mucosa, *Am J Physiol* **67** 124, 1923

20 Ivy, A. C., and Javois, A. J. Contributions to the Physiology of Gastric Secretion. VI. The Stimulation of Gastric Secretion by Amines and Other Substances, *Am J Physiol* **71** 604, 1925

21 Hess, W. R., and Gundlach, R. Der Einfluss des Adrenalins auf die Sekretion des Magensaftes, *Arch f d ges Physiol* **185** 122, 1920

22 Rothlin. Communication, Internat Physiol Congress, Paris, 1920, cited from Lim (footnote 18)

23 Fuse, Y. Studien über die Magensaftes. III. Ueber den Einfluss von Adrenalin auf die Sekretion des Magensaftes, *Mitt d med Gesellsch Chiba* **6** 185, 1928

24 Sirotinin, G. W. Ueber die Wirkung des Adrenalins auf die Sekretion des Magensaftes aus dem nach Heidenhain isolierten kleinen Magendes Hundes, *Ztschr f d ges exper Med* **40** 90, 1924

25 Collazo, J. A., and Dobreff, M. Die Beeinflussung der äusseren Sekretion des Pankreas durch Insulin nebst einer Bemerkung über die Wirkung desselben auf die Harnausscheidung, *München med Wchnschr* **71** 1678, 1924

26 Ono, J. Ueber die Beeinflussung der äusseren Sekretion des Pankreas durch Insulin, *Verhandl d Japan Gesellsch f inn Med* **23** 77, 1926

27 Yoshida, T. Untersuchungen an Menschen über den Einfluss des Insulins auf die äussere Sekretion des Pankreas, *Verhandl d Japan Gesellsch f inn Med* **23** 77, 1926

28 Arima, E. Ueber den Einfluss des Insulins auf das Pankreas, *Verhandl d Japan Gesellsch f inn Med* **23** 78, 1926

29 Footnote 7. Gytoku, K., and Kuramochi, K. The Influence of Insulin on the External Secretion of Pancreas, *Mitt d med Gesellsch, Tokyo* **41**. 3231, 1927

Heimann<sup>30</sup> obtained only negative results. Brugsch and Horstels<sup>31</sup> found that insulin caused an increased secretion of bile. Dobreff,<sup>32</sup> Sakurai,<sup>15</sup> Nitzescu<sup>33</sup> and others confirmed this. D  tre and Siv  ,<sup>34</sup> Terashima,<sup>35</sup> Fernando and De Carvalho<sup>36</sup> and others demonstrated that insulin is a vigorous excitant of gastric secretion, though Collazo and Dobreff<sup>37</sup> found quite the contrary result.

Extracts of various tissues were also investigated by various workers as to influence on the secretion of the digestive juices. The results, in general, were not so remarkable and unanimous, however, as those found with the use of epinephrine and insulin.

In view of the foregoing data, it might be considered, in general, that epinephrine inhibits the secretion of digestive juices and that insulin accelerates it. The mechanism of this inhibitory and excitatory action, however, is unknown. The purpose of this study was to solve, so far as possible, the *modus operandi* of the regulatory mechanism of the secretion of the digestive juices, so necessary for the welfare of man and animals.

#### METHODS

The activity of the secretion of pancreatic juice was shown by multiplying the amount of each half hour specimen by the enzymatic activity, which was determined by the method described in the first paper of this series<sup>38</sup>. The esti-

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30 Lambert, M., and Hermann, H. *Insuline et suc pancreatique*, *Compt rend Soc de biol* **92** 43, 1925.

31 Brugsch, T., and Horstels, H. *Ueber die Leber als Ausscheidungsorgan und   ber die Wirkung der Choleretica, insbesondere des Atophans*, *Med Klin* **20**:661, 1924.

32 Dobreff, M. *Experimentelle Untersuchungen   ber die Wirkung des Insulins auf die   ussere Sekretion der Verdauungsdr  sen. II. Ueber den Einfluss des Insulins auf die Gallenabsonderungsf  higkeit*, *Biochem Ztschr* **154** 364, 1924.

33 Nitzescu, I. I. *L'insuline et la secretion biliare*, *Compt rend Soc de biol* **95** 773, 1926.

34 D  tre, L., and Siv  , R. *Insulin und Magensekretion*, *Ztschr f d ges exper Med* **46** 594, 1925.

35 Terashima, S. *The Influence of Insulin on the Secretion of Gastric Juice*, *Ejishimbun*, 1927, no 1208, p 343.

36 Fernando, F., and de Carvalho, A. *Sur le m  canisme de l'action de l'insuline sur la s  cr  tion gastrique*, *Compt rend Soc de biol* **96** 1327, 1927.

37 Collazo, J. A., and Dobreff, M. *Experimentelle Untersuchungen   ber die Wirkungen des Insulins auf die   ussere Sekretion der Verdauungsdr  sen. I. Insulinwirkung auf die Sekretion des Magensaftes*, *Biochem Ztschr* **154** 349, 1924.

38 Okada, S., Sakurai, E., Imazu, T., and Kuramochi, K. *Pancreatic Function. I. The Quantitative Estimation of Pancreatic Secretion*, *Arch Int Med* **42** 270 (Aug) 1928.



mation of the activity of the secretion of bile was carried out by determining the amount of bile pigment in each half hour specimen, in the manner described in the first paper. For the estimation of the content of bile acids in the duodenal return, we employed Hay's sulphur flower test,<sup>39</sup> which, though not so precise as might be wished, still gave results sufficiently consistent for practical purposes. The duodenal return was diluted until granules of depurated sulphur did not sink to the bottom. The measure of this dilution is mentioned as the "bile acids number." This number was multiplied by the amount of each half hour specimen and indicated as the degree of secretion of bile acids. The gastric juice was collected every fifteen minutes by continuous suction through the Rehfuß tube being used. The presence of free hydrochloric acid was tested for with congo paper, and the total acidity was estimated with phenolphthalein as indicator. The peptic activity was estimated by Fuld and Levison's edestin method<sup>40</sup>. The blood sugar content was estimated partly by Bang's new micromethod<sup>41</sup> and partly by Hagedorn and Jensen's method<sup>42</sup>.

#### EXPERIMENTS

At first, it seemed necessary to try an experiment as to whether insulin in reality provokes gastric, pancreatic and biliary secretions and whether epinephrine inhibits them. We passed one tube into the stomach (in human subjects) and another tube into the duodenum, and, after a hypodermic injection of insulin or of epinephrine hydrochloride, collected the gastric and the duodenal contents simultaneously and analyzed the collected juices. The results confirmed the prevailing data except as to the influence of epinephrine on the gastric secretion, which was not so decisive. We also found that ephedrine has an inhibitory influence on the secretion of the digestive juices. The increased secretion of the gastric and of the pancreatic juices after an injection of insulin was manifest both in the amounts and in the concentrations. These results were especially marked when a pronounced hypoglycemia occurred, following almost parallel to this, but were nearly negative when hypoglycemia failed. The decrease of the secretion of these juices after the injection of epinephrine went parallel with the hyperglycemia, and was followed by an increase of secretion when a reactive hypoglycemia occurred.

39 Hay, cited by Lowenberg, W., Nauenberg, W., and Noah G. Vergleichende Leberfunktionsprüfungen, *Klin. Wchnschr.* **6** 445, 1927, and by Lepelne. Vergleichende Untersuchungen über den Bilirubin- und Gallensaurestoffwechsel beim Lebergesunden, Leberkranken und Neugeborenen, *ibid.* **1** 2031, 1922.

40 Fuld, E., and Levison, L. A. Die Pepsinbestimmung mittels der Edestinprobe, *Biochem. Ztschr.* **6** 473, 1907.

41 Bang, I. Mikromethoden zur Blutzuckeruntersuchung, Munich and Wiesbaden, J. F. Bergmann, 1922.

42 Hagedorn, H. C., and Jensen, B. N. Zur Mikrobestimmung des Blutzuckers mittels Ferricyanid, *Biochem. Ztschr.* **135** 46, 1923, Die Ferricyanidmethode zur Blutzuckerbestimmung II, *ibid.* **137** 92, 1923.

As the gastric secretion is profuse after an injection of insulin, the stimulating influence on the pancreatic secretion might be induced, partly at least, by the secretin mechanism. It seemed necessary, therefore, to decide whether there is also a primary stimulation. To solve this problem, we made observations on patients with achylia gastrica, but we encountered difficulty when marked hypoglycemia occurred, for this, in most cases of achylia gastrica, caused a profuse secretion of gastric

TABLE 1—*Results of the Analyses of the Contents of the Stomach and the Duodenum of a Man, Aged 22 A, When Stimulants of Secretion Had Not Been Administered*

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Duodenal Return							
		Gastric Juice		Amount of Juice, Cc	Trypsin Kilo- Units (Amount × Activity)	Amylase Kilo- Units (Amount × Activity)	Lipase Kilo- Units (Amount × Activity)	Bile Pigment (Dilution × Amount)	Bile Acids (Dilution × Amount)
		Free HCl	Total Acid ity						
1/4		35	43						
1/2				41 0	13,120	23,452	46,740	2,665	22,550
3/4		45	54						
1		58	64	33 0	6,600	15,708	36,300	2,310	17,150
1 1/4		51	58						
1 1/2		42	53	21 0	6,720	1,848	21,672	1,050	10,500
1 3/4		43	48						
2		62	74	7 5	3,750	5,010	7,050	450	5,250
2 1/4		64	72						
2 1/2		49	58	22 0	11,000	15,135	25,080	2,140	16,500
2 3/4		64	72						
3		100	106	29 0	14,500	21,721	24,360	1,450	14,500
Total				153 5	55,690	82,875	161,202	9,995	86,450

*B Following a Hypodermic Injection of Insulin (Toronto), 10 Units\**

Fasting	0 086	64	69	20 0	6,400	8,160	16,000	4,080	39,000
Following an injection of insulin									
1/4		24	31						
1/2	0 078	78	82	6 0	1,200	3,546	2,340	828	9,300
3/4		75	81						
1	0 069	103	108	29 5	23,700	67,585	33,630	15,340	103,250
1 1/4		121	125						
1 1/2	0 044	124	131	55 0	27,500	90,475	35,200	9,680	68,750
1 3/4		119	123						
2	0 056	103	113	38 5	19,250	31,300	17,248	5,852	46,200
2 1/4		126	130						
2 1/2	0 053	127	133	31 5	15,750	58,653	7,434	5,040	37,900
2 3/4		101	112						
3	0 054	44	48	31 0	15,500	33,790	23,764	4,960	33,750
Total				191 5	102,800	285,349	140,618	41,700	304,050

\* In this and following tables one example is shown, though the same experiment was tried many times until we were confident of the results.

juice rich in free hydrochloric acid (as shown in table 2). Finally, we discovered cases of cancer of the stomach in which, after an injection of insulin, the gastric juice remained alkaline during the course of the collection, and we then were able to show a marked increase in pancreatic and biliary secretions. Therefore, it was proved that insulin stimulates primarily the pancreatic and biliary secretions. It was most important then to decide whether hypoglycemia and the increased secretion of the digestive juices are induced independently by insulin, or

TABLE 2—Results of the Analyses of the Contents of the Duodenum of a Man, Aged 20, with Achylia Gastrica A, When Stimulants of Secretion Were Not Administered

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		Duodenal Return				
		Free HCl	Total Acidity	Amount of Juice, Cc	Trypsin	Amylase	Lipase	Bile Pigment (Dilution × Amount)
					Kilo- Units (Amount × Activity)	Kilo- Units (Amount × Activity)	Kilo- Units (Amount × Activity)	
½				53.0	26,500	78,228	85,330	901
1				30.0	21,000	46,710	96,600	7,800
1½				23.0	28,750	40,020	57,040	7,360
2				1.0	320	1,319	1,150	48
2½				3.5	1,120	6,265	1,197	25
3				9.0	4,500	16,920	7,020	415
Total				119.5	83,190	189,462	248,337	16,549

*B Following a Hypodermic Injection of Insulin (Toronto), 11 Units*

Fasting Following an in- jection of insulin	0 074	0	2					
1/2	0 062	0	8	43 0	13,631	61,361	27,778	4,730
1	0 058	0	2	21 0	16,800	37,653	11,424	2,100
1 1/2	0 058	36	48	35 0	70,000	67,585	80,500	18,900
2	0 048	44	53	41 0	51,280	82,902	147,600	19,630
2 1/2	0 047	26	36	29 0	36,250	53,157	37,700	11,020
3	0 036	26	34	13 0	16,250	26,689	9,100	4,420
Total				182 0	204,181	329,347	314,102	60,850

TABLE 3—Results of the Analyses of the Contents of the Stomach and the Duodenum of a Man, Aged 28, Following a Hypodermic Injection of Epinephrine Hydrochloride, 1 Cc

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Duodenal Return							
		Gastric Juice		Amount of Juice, Cc	Trypsin Kilo- Units (Amount × Activity)	Amylase Kilo- Units (Amount × Activity)	Lipase Kilo- Units (Amount × Activity)	Bile Pigment (Dilution × Amount)	Bile Acids (Dilution × Amount)
		Free HCl	Total Acid- ity						
Fasting									
¼	0.083	26	30						
½		44	52	26.8	5,360	19,912	6,378	348	4,020
¾		20	32						
1	0.088	18	28	6.8	1,360	8,439	1,020	54	680
Following an injection of epinephrine									
¼	0.129	16	26						
½	0.127	24	34	0	0	0	0	0	0
¾	0.130	24	34						
1	0.144	22	34	0.8	320	2,059	39	4	64
1¼	0.154	16	30						
1½	0.132	16	32	2.6	260	3,401	572		
1¾	0.109	14	28						
2	0.113	14	24	2.0	1,250	6,174	384		
2¼	0.086	0	16						
2½	0.079	3	19	2.7	1,688	7,679	410		
2¾	0.069	6	22						
3	0.058	0	13	19.2	24,000	55,238	24,100	5,568	23,040

whether hypoglycemia has any connection with this increased secretion. A marked hypoglycemia was produced in human subjects by insulin, and when the gastric, pancreatic and biliary secretions became profuse, injections of dextrose solution of different concentrations were made intravenously, intraduodenally or through the rectum. A prompt and marked inhibition of the secretion of these juices occurred simultaneously with the increase of the sugar content of the blood regardless of the concentration and locality of the sugar introduced. Profuse

TABLE 4—*Results of the Analyses of the Contents of the Duodenum of a Girl, Aged 19 A, Following the Intraduodenal Injection of Water, 200 Cc*

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Duodenal Return					
		Amount of Juice, Cc	Trypsin Kilo- Units (Amount × Activity)	Amylase Kilo- Units (Amount × Activity)	Lipase Kilo- Units (Amount × Activity)	Bile Pigment (Dilution × Amount)	Bile Acids (Dilution × Amount)
Fasting							
1/2	0.084	11.4	9,120	20,657	13,817	741	9,120
1	0.086	23.0	18,400	41,676	33,120	1,196	18,400
Following intraduodenal injection of water							
1/2	0.088	28.5	9,120	16,502	15,390	570	9,120
1	0.082	28.8	14,400	32,976	21,082	2,182	18,400
1 1/2	0.085	31.0	24,800	50,096	45,570	1,922	13,475
2	0.083	26.5	13,250	27,984	25,838	1,087	21,600
2 1/2	0.084	36.0	18,000	12,708	27,072	1,008	23,350
3	0.083	18.0	12,400	22,062	23,162	414	18,550
Total of 3 hours		168.8	91,970	162,328	158,114	7,183	107,495
<i>B Following the Intraduodenal Injection of Ephedrine, 0.04 Gm</i>							
Fasting							
1/2	0.090	11.0	6,875	17,336	14,080	385	4,950
1	0.089	19.2	7,680	26,923	19,584	422	7,680
Following injection of ephedrine							
1/2	0.092	7.3	1,825	8,015	4,083	124	1,825
1	0.092	1.8	450	2,372	972	32	450
1 1/2	0.091	0.7	112	993	231	10	175
2	0.100	1.1	110	1,200	264	7	165
2 1/2	0.094	3.1	310	2,623	471	6	310
3	0.081	7.0	4,375	16,380	8,512	294	4,200
3 1/2	0.086	1.8	720	3,296	1,065	45	570
4	0.085	0.9	360	1,510	230	11	180
Total of 3 hours		21.0	7,182	31,583	14,538	473	7,125

secretion was caused again when the hypoglycemia recurred. Therefore, it was proved that hypoglycemia, if it does not alone stimulate the secretion of these juices, does so when insulin is injected.

It was, then, of interest to determine, if possible, whether this stimulation occurs peripherally in the tissue cells or centrally in the centrum of the nervous system. An injection of atropine caused a distinct inhibition of the secretion of the juices induced by insulin, hence it was assumed that hypoglycemia exerts its stimulating effect on the centrum of the secretory nerve and that the stimulus is transmitted to the acting tissue cells through the parasympathetic nervous system. This led to the question whether hypoglycemia, in general,

TABLE 5—Results of the Analyses of the Contents of the Stomach and Duodenum in a Man, Aged 50, with Cancer of the Stomach A, When No Stimulants Had Been Administered

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice	Duodenal Return				
			Amount of Juice, Cc	Trypsin Kilo-Units (Amount × Activity)	Amylase Kilo-Units (Amount × Activity)	Lipase Kilo-Units (Amount × Activity)	Bile Pigment (Dilution × Amount)
½		Alkaline	24 0	12,000	35,208	6,120	1,964
1		Alkaline	17 0	13,600	17,034	9,775	2,890
1½		Alkaline	20 0	16,000	25,820	10,800	3,200
2		Alkaline	23 0	11,500	24,932	9,660	2,484
2½		Alkaline	23 0	18,400	31,142	23,475	4,787
3		Alkaline	14 0	11,200	18,396	13,440	4,480
Total			121 0	82,700	152,532	64,150	17,838

*B Following a Hypodermic Injection of Insulin (Toronto), 10 Units*

Fasting	0 078	Alkaline					
Following an injection of insulin							
½	0 066	Alkaline	17 5	8,750	24,658	17,150	3,500
1	0 067	Alkaline	22 0	17,600	34,716	13,640	3,740
1½	0 064	Alkaline	51 0	40,800	62,935	55,335	11,010
Following an intra-venous injection of 25% dextrose, 50 cc							
2	0 070	Alkaline	18 0	9,000	19,584	13,680	3,420
2½	0 051	Alkaline	31 0	24,800	36,177	31,558	6,820
3	0 049	Alkaline	46 0	36,800	58,650	57,270	10,580
Total			185 5	137,750	236,720	188,633	39,070

TABLE 6—Results of the Analyses of the Contents of the Stomach and the Duodenum Following a Hypodermic Injection of Insulin (Toronto), 12 Units, and an Intravenous Injection of Dextrose in a Man,† Aged 20‡

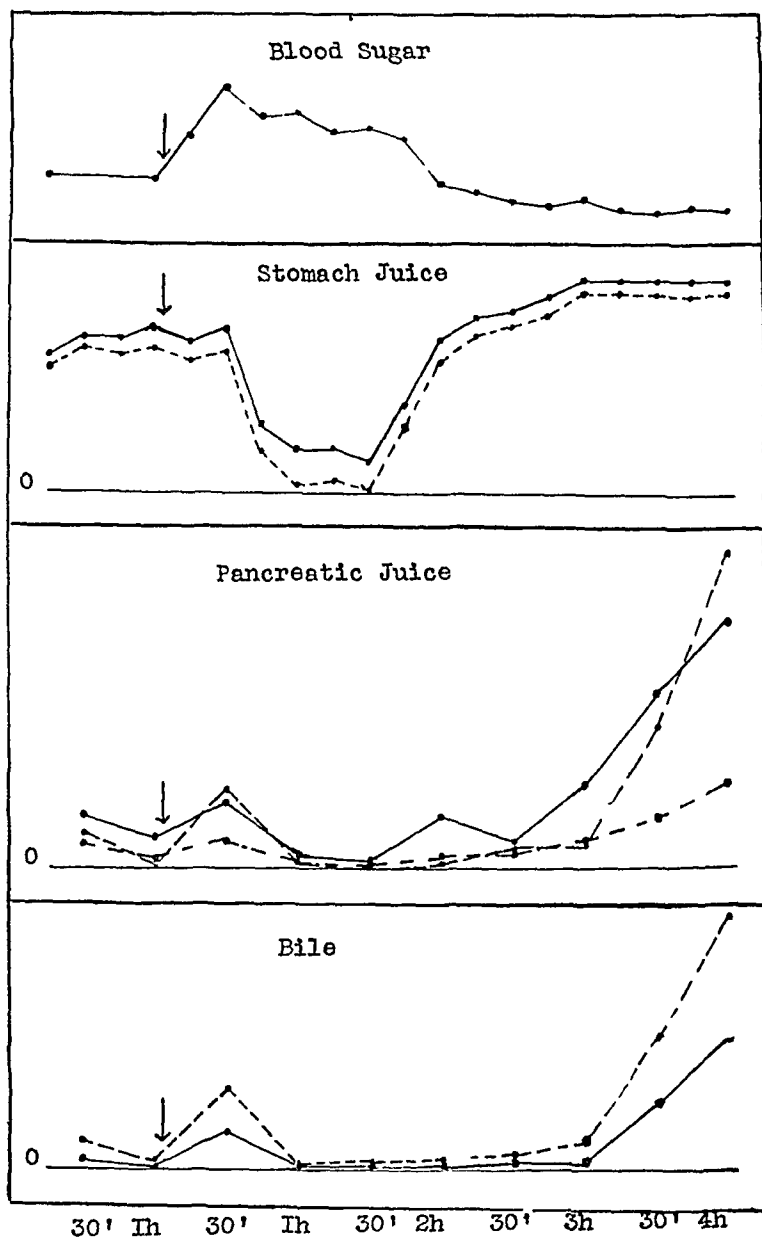
Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		Amount of Juice, Cc	Duodenal Return			
		Free HCl	Total Acidity		Trypsin	Amylase	Lipase	Bile
					Kilo- Units (Amount × Activity)	Kilo- Units (Amount × Activity)	Kilo- Units (Amount × Activity)	Pigment (Dilution × Amount)
Fasting	0 079	Alkaline						
Following an injection of insulin + an intravenous injection of 25 per cent dextrose, 50 cc *								
1½	0 065	Alkaline		8 0	2,536	9 560	7,080	1,248
1	0 060	Alkaline		15 5	4,914	24,366	5,425	961
Following an intravenous injection of 25 per cent dextrose, 50 cc *								
1½	0 048	0	12	11 5	5,750	17,331	25,300	2,875
2	0 044	22	36	60 0	75,000	91,920	187,200	37,200
Following an intravenous injection of 25 per cent dextrose, 50 cc *								
2½	0 058	0	14	26 5	13,250	34,477	60,950	5,865
3	0 055	8	26	47 0	37,600	72,850	96,350	8,630
Total				168 5	139,050	250,504	382,305	56,779

\* After each injection of dextrose the secretion stopped thoroughly for a while

† Same patient as in table 2

‡ Urine 320 cc, urinary sugar 0.46 per cent = 1.47 Gm

stimulates the secretion of the digestive juices and whether hyperglycemia inhibits this secretion. It was desirable to solve this question without using insulin or epinephrine. For this purpose, we introduced a tube into the stomach, a tube into the duodenum and another tube into the jejunum. After collection of the gastric and the duodenal contents for a time, a 25 per cent solution of dextrose in the



The results of analyses of the gastric, pancreatic and biliary juices following an intraduodenal injection of 25 per cent dextrose in the amount of 1 Gm per kilogram of body weight, in a man, aged 29 (table 8, A). The correlation between the activity of the secretion of the digestive juices and the sugar content of the blood may be noted. The arrow indicates the injection of dextrose. In the curves for the gastric juice, the straight line indicates total acidity, and the dotted line free hydrochloric acid. In the curves for the pancreatic juice, the straight line indicates amylase, the dotted line lipase and the dash and dot line trypsin. In the curves for bile, the straight line indicates pigment ( $\times 10$ ) and the dotted line acids.

amount of 1 Gm per kilogram of body weight was introduced into the jejunum and the collection of the digestive juices was continued. Often there was an initial increase of the secretion in the first fifteen to thirty minutes after the injection, most likely owing to a reflex mechanism. Hyperglycemia, after the resorption of the dextrose, however, stopped the pancreatic and biliary secretions almost entirely, and the gastric contents became achlorhydric. The hyperglycemia continued for about one and three quarters hours, and at this point the secretion of the digestive juices stopped almost completely. Following the hyperglycemia, a reactive

TABLE 7—*Results of the Analyses of the Contents of the Stomach and the Duodenum Following a Hypodermic Injection of Insulin (Toronto), 10 Units, and Atropinum Sulfuricum, 15 Mg, in a Man,† Aged 22*

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		Amount of Juice Cc	Duodenal Return				
		Free HCl	Total Acidity		Trypsin Kilo Units (Amount × Activity)	Amylase Kilo-Units (Amount × Activity)	Lipase Kilo Units (Amount × Activity)	Bile Pigment (Dilution × Amount)	Bile Acids (Dilution × Amount)
Fasting	0.088	37	42						
Following an injection of insulin									
1/4		27	31						
1/2	0.081	4	10	3.4	1,700	2,689	2,856	204	2,380
Following an injection of atropine *									
3/4		6	10						
1	0.065	14	20	4.6	920	3,505	2,875	216	2,300
1 1/4		No juice							
1 1/2	0.060	8	14	20.0	6,400	17,340	41,800	4,200	23,000
1 3/4		62	67						
2	0.066	116	124	43.0	21,500	75,250	80,496	7,310	45,150
2 1/4		127	132						
2 1/2	0.063	109	118	40.0	12,800	50,560	50,560	4,000	20,000
2 3/4		130	137						
3	0.072	118	125	37.0	18,500	54,649	53,250	6,125	22,200
Total				148.0	61,820	212,993	231,867	22,055	115,030

\* After the injection of atropine, the secretion of the gastric and the duodenal juices stopped thoroughly for a while, and fifty six minutes after the injection, the secretion of both began again, so that it was markedly less in the first hour and a half after the injection of insulin in comparison with that recorded in table 1, B. Thereafter an effect of the atropine was not expected.

† Same patient as in table 1.

hypoglycemia was evoked, sometimes being as low as 0.059 to 0.053 per cent, accompanied by a profuse secretion of the digestive juices. Injections of dextrose of the same amount in concentrations of 25, 20 or 5 per cent showed the same results. Intravenous injections of nearly the same amounts of dextrose had almost the same effect, except that they failed to produce the initial increase of secretions. The diminution of the gastric secretion was manifested more in amount than in acidity when a hypertonic dextrose solution was administered intravenously. It might be especially emphasized that an isotonic or rather a somewhat hypotonic solution of dextrose had the same inhibitory influence on the secretion of digestive juices, if the amount was sufficient. The

same experiments were repeated, and at the stage of complete cessation of the secretion as a result of the hyperglycemia (thirty minutes after the injection of dextrose into the duodenum) we tried injections of 100

TABLE 8—Results of the Analyses of the Contents of the Stomach and the Duodenum in a Man, Aged 29 A, Following the Intraduodenal Injection of 25 Per Cent Dextrose in the Amount of 1 Gm Per Kilogram of Body Weight

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		Amount of Juice, Cc	Duodenal Return					
		Free HCl	Total Acidity		Trypsin Kilo-Units (Amount × Activity)	Amylase Kilo-Units (Amount × Activity)	Lipase Kilo-Units (Amount × Activity)	Bile Pigment (Dilution × Amount)	Bile Acids (Dilution × Amount)	
										Amount of Juice, Cc
Fasting										
1/4	0 098	70	77	46 0						
1/2		80	86	23 0	38 0	12,160	29,032	17,328	494	17,100
3/4		77	86	26 0						
1	0 096	80	92	23 6	10 0	4,000	14,950	2,500	40	1,000
Following an injection of dextrose										
1/4	0 120	74	84	5 0						
1/2	0 148	78	90	25 4	65 0	13,000	33,995	41,600	2,080	45,500
3/4	0 131	22	37	6 8						
1	0 133	4	24	6 8	4 8	1,200	4,042	1,286	29	960
1 1/4	0 122	6	24	7 8						
1 1/2	0 124	0	16	6 4	1 0	160	821	270	3	100
1 3/4	0 119	38	48	26 0						
2	0 092	72	84	12 4	9 0	5,625	27,099	1,890	54	1,800
2 1/4	0 089	86	96	10 0						
2 1/2	0 082	91	101	34 0	4 8	6,000	11,746	6,960	264	2,760
2 3/4	0 080	98	108	43 0						
3	0 083	110	118	24 4	28 0	14,000	46,844	12,600	484	12,600
3 1/4	0 079	110	118	23 6						
3 1/2	0 077	109	117	18 0	55 0	27,500	96,580	77,220	3,740	74,250
3 3/4	0 080	108	118	22 0						
4	0 077	110	116	21 4	94 0	47,000	136,770	174,370	7,144	141,000
<i>B, Following the Intraduodenal Injection of Dextrose and a Hypodermic Injection of Atropinum Sulfuricum</i>										
Fasting										
1/4	0 099	23	28	20 0						
1/2		51	59	12 4	46 5	7,440	21,111	5,812	47	930
3/4		38	47	11 6						
1	0 097	47	53	9 4	24 0	9,600	52,176	5,520	72	2,400
Following an injection of 25% dextrose in the amount of 1 Gm per kilogram of body weight										
1/4	0 123	46	55	31 6						
1/2	0 152	6	17	10 0	63 0	31,500	56,637	84,420	3,402	5,985
3/4	0 146	0	6	8 0						
1	0 137	0	3	20 0	5 0	1,250	4,560	2,100	70	2,000
1 1/4	0 129	0	4	9 0						
1 1/2	0 108			0	17 0	6,800	46,869	4,250	51	1,700
1 3/4	0 102	7	15	6 6						
Following an injection of atropine, 1 mg *										
2	0 098	44	53	9 4	23 5	29,375	57,669	21,040	893	14,450
2 1/4	0 089	84	92	2 6						
2 1/2	0 084	70	76	2 4	1 0	625	1,762	485	30	550
2 3/4	0 086	91	95	12 6						
Following an injection of atropine, 1 mg *										
3	0 078	63	67	13 4	4 6	1,840	8,758	1,748	51	1,840
3 1/4	0 069	81	85	3 4						
3 1/2	0 067	50	60	4 6	1 3	520	2,652	273	9	325
3 3/4	0 064	70	78	1 8						
4	0 065	91	95	5 0	1 6	400	3,165	376	11	400

\* The effect of atropine was especially legible from twenty to fifty minutes after injection

cc of 0.2 per cent hydrochloric acid or 3 cc of ether into the duodenum. This resulted in a little secretion of pancreatic juice and bile. When dextrose was administered intravenously, this intraduodenal stimulation was more effective (perhaps owing in this case to the absence of a fore-



going initial evacuation of the gall and the pancreatic tracts including the gallbladder) Therefore, we proved that hypoglycemia, in general, stimulates the secretory nervous centrum, that hyperglycemia inhibits it and that the stimulus is transmitted through the parasympathetic nervous system to the reacting tissue cells, while the inhibitory impulse is most likely transmitted through the sympathetic nervous system. This process is as natural as well as important one for the welfare of mankind. When too much nourishment is absorbed, so that hyperglycemia is induced, the secretion of the digestive juices is arrested by an inhibitory stimulus, and further digestion and resorption are inhibited until the normal level of the sugar content of the blood is restored.

TABLE 9—*Results of the Analyses of the Contents of the Stomach and the Duodenum Following the Intraduodenal Injection of 5 Per Cent Dextrose in the Amount of 0.8 Gm Per Kilogram of Body Weight in a Youth, Aged 19*

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		Duodenal Return						
		Free HCl	Total Acidity	Amount of Juice, Cc	Amount of Juice, Cc	Trypsin	Amylase	Lipase	Bile Pigment	Bile Acids
						Kilo-Units (Amount × Activity)	Kilo-Units (Amount × Activity)	Kilo-Units (Amount × Activity)	(Dilution × Amount)	(Dilution × Amount)
Fasting										
1/4	0 103	38	45	11 3						
1/2		32	44	12 2	15 0	7,500	29,895	7,650	450	8,250
3/4		32	44	10 0						
1	0 095	28	44	11 5	23 5	18,800	82,250	9,400	2 115	30,550
Following an injection of dextrose										
1/4	0 135									
1/2	0 176	14	27	18 0	60 0	6,000	36,900	42,480	3,900	45,000
3/4	0 161	0	8	5 3						
1	0 126	Neutral		5 5	4 6	920	6,178	2,277	161	2,760
1 1/4	0 103	Alkaline		9 0						
1 1/2	0 094	Alkaline		3 8	1 4	280	3,916	56	21	420
1 3/4	0 093	19	32	9 5						
2	0 089	72	78	19 5	25 0	20,000	87,725	21,875	1,700	40,000
2 1/4	0 085	80	89	18 0						
2 1/2	0 087	78	83	31 0	24 0	12,000	49,680	27,216	1,680	21,600
2 3/4	0 085	70	80	7 8						
3	0 082	68	72	13 0	13 6	10,880	4,124	19,040	884	12,240
3 1/4	0 084	85	96	27 5						
3 1/2	0 087	98	105	51 5	42 0	33,600	72,282	36,288	4,830	75,600
3 3/4	0 094	97	106	37 0						
4	0 093	97	106	26 0	13 2	10,560	31,442	5,808	1,386	21,780

The test breakfast induced a markedly diminished secretion of acid in the stomach at the stage of hyperglycemia in comparison with that induced in fasting. The motility of the stomach was also inhibited, and the remnants of bread were detectable by fractional suction after a test breakfast for a longer period (for example, for two and a quarter hours in hyperglycemia, as compared with less than one hour at the time of fasting). Hypoglycemia is accompanied by a sensation of hunger, which causes one to take food eagerly and digestion takes place promptly by reason of the profuse secretion of the digestive juices. Resorption, accordingly, occurs to meet the needs, while hyperglycemia causes a full and distended feeling in the epigastric region which, in turn, causes one to refuse food. When, however, foods are already

TABLE 10—Results of the Analyses of the Contents of the Stomach and the Duodenum in a Man, Aged 22 \* A, Following the Intraduodenal Injection of 25 Per Cent Dextrose in the Amount of 1 Gm Per Kilogram of Body Weight and 0.2 Per Cent Hydrochloric Acid, 100 Cc

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		Amount of Juice, Cc	Duodenal Return				
		Free HCl	Total Acidity		Trypsin Kilo-Units (Amount × Activity)	Amylase Kilo-Units (Amount × Activity)	Lipase Kilo-Units (Amount × Activity)	Bile Pigment (Dilution × Amount)	Bile Acids (Dilution × Amount)
Fasting									
1/4	0.086	62	72						
1/2		74	79	11.0	3,520	8,250	8,710	1,210	8,230
3/4		80	86						
1	0.085	71	77	11.0	3,520	20,163	4,048	2,200	20,900
Following the injection of dextrose									
1/4	0.115	16	24	44.0	2,200	27,500	29,040	6,160	35,200
1/2	0.150			2.0	200	1,212	800	170	1,300
Following the injection of hydrochloric acid									
3/4	0.151	Very weak +							
1	0.152	16	20	6.4	320	2,528	2,976	409	3,200
1 1/4	0.128	18	22						
1 1/2	0.107	17	21	8.8	440	4,585	2,816	79	1,760
1 3/4	0.091	16	22						
2	0.078	15	22	2.8	56	1,252	844	14	250
2 1/4	0.053	12	20						
2 1/2	0.057	3	10	14.6	1,460	27,463	11,680	734	7,300
2 3/4	0.063	2	8						
3	0.092	0		45.0	14,400	50,310	23,080	10,350	90,000
3 1/4	0.081	20	30						
3 1/2	0.075	40	50	10.8	2,160	14,029	5,184	1,836	16,740
3 3/4	0.078	54	69						
4	0.093	60	71	25.6	8,192	42,701	11,264	3,120	46,080

B, Following the Intraduodenal Injection of 25 Per Cent Dextrose in the Amount of 1 Gm Per Kilogram of Body Weight and Ether, 3 Cc

Fasting									
1/4	0.089	78	86						
1/2		94	100	14.3	4,576	27,141	12,584	1,287	7,150
3/4		94	104						
1	0.090	90	98	12.4	6,200	14,804	11,656	434	3,720
Following an injection of dextrose									
1/4	0.123	90	98						
1/2	0.136	68	72	12.2	2,440	11,326	2,782	73	1,220
Following an injection of ether									
3/4	0.144	24	34						
1	0.132	24	34	20.5	3,280	24,231	6,765	0	0
1 1/4	0.121	16	25						
1 1/2	0.119	15	25	7.0	1,120	7,462	1,365	0	140
1 3/4	0.101	8	18						
2	0.088	10	20	7.6	3,040	9,287	1,596	266	3,040
2 1/4	0.061	6	14						
2 1/2	0.069	8	18	32.0	16,000	36,233	16,000	7,360	38,400
2 3/4	0.063	10	20						
3	0.063	20	30	44.0	22,000	76,164	63,140	7,920	44,000
3 1/4	0.065	32	46						
3 1/2	0.075	8	20	16.6	5,312	25,265	19,920	1,072	9,130
3 3/4	0.071	50	60						
4	0.070	70	78	4.6	920	4,278	1,863	27	690

\* Same patient as in table 1.

present in the digestive tract, direct digestion and resorption do not occur, owing to the inhibition of the secretion so long as hyperglycemia continues. Since hypoglycemia and hyperglycemia induce humorally excitatory or inhibitory impulses to the secretory centrum, and since from this centrum the stimuli are transmitted through the autonomic nervous system to the acting tissue cells, this process might be called the "humoroneural regulation of the secretion of digestive juices," thus establishing the theory that we have advanced. The secretion of saliva is excepted from this regulation, the mechanism of which is entirely nervous, as was noticed by previous workers.

TABLE 11—*Results of the Analyses of the Contents of the Stomach\* and the Duodenum Following the Intravenous Injection of 25 Per Cent Dextrose in the Amount of 0.7 Gm Per Kilogram of Body Weight in a Man, Aged 32, Weighing 53 Kg*

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Amount of Juice, Cc	Duodenal Return				
			Trypsin Kilo-Units (Amount × Activity)	Amylase Kilo-Units (Amount × Activity)	Lipase Kilo-Units (Amount × Activity)	Bile Pigment (Dilution × Amount)	Bile Acids (Dilution × Amount)
Fasting							
½	0.095	30.0	15,000	71,400	18,000	1,050	33,000
1	0.096	5.2	2,600	9,630	3,536	680	8,060
Following an injection of dextrose							
¼	0.209						
½	0.232	0	0	0	0	0	0
¾	0.219						
1	0.190	1.0	0	435	344	8	100
1¼	0.164						
1½	0.132	0.7	0	305	143	5	70
1¾	0.117						
2	0.099	1.0	0	641	280	2	50
2¼	0.099						
2½	0.090	12.0	9,600	26,232	25,920	3,120	33,600
2¾	0.090						
3	0.074	10.8	3,456	10,152	13,099	594	7,560
3¼	0.081						
3½	0.092	11.8	9,440	22,621	32,450	9,912	64,900
3¾	0.093						
4	0.086	8.3	6,640	17,704	10,292	2,075	14,940

\* All fractions of gastric juice remained alkaline during the course of the experiment.

THE HUMORONEURAL REGULATION IN DIABETES MELLITUS

As a result of these studies, consideration had to be given to whether this regulation also plays a part in diabetes mellitus, a pathologic condition that shows a high degree of hyperglycemia even in fasting. As we reported in the second paper of this series, there are cases of diabetes mellitus in which the external pancreatic secretion is extremely disturbed, while in others it remains normal. According to the prevailing views, the gastric and the biliary secretions are not necessarily disturbed in diabetes mellitus. It was therefore necessary to determine whether the humoroneural regulation is not in force in such a disturbed regulation of the carbohydrate metabolism as that in diabetes mellitus or

TABLE 12—Results of the Analyses of the Gastric Juice of a Youth, Aged 19 A, Following the Intraduodenal Injection of 20 Per Cent Dextrose in the Proportion of 1 Gm Per Kilogram of Body Weight, and Test Breakfast (Bread, 35 Gm, Water, 400 Cc), B, Following the Test Breakfast

Times at Which Specimens Were Collected, Hours	A					B				
	Blood Sugar, per Cent	Gastric Juice			Blood Sugar, per Cent	Gastric Juice				
		Free HCl	Total Acidity	Pepsin Units		Free HCl	Total Acidity	Pepsin Units		
Fasting										
1/4	0 096	0	3	125	0 114	8	22	90		
1/2		3	21			9	26			
3/4		25	37			8	20			
1		30	42	400	0 115	4	12	90		
Following an injection of dextrose										
1/4	0 098	24	30	400						
1/2	0 153	Alkaline								
Following a test breakfast										
1/4	0 167	Neutral		15	0 117	14	23	60		
1/2	0 154	Neutral		20	0 124	18	28	60		
3/4	0 128	Neutral		50	0 121	19	34	60		
1	0 103	6	12	80	0 120	16	32	30		
1 1/4	0 105	17	23		0 115	28	44			
1 1/2	0 107	22	32	100	0 107	29	44			
1 3/4	0 103	22	32		0 105	56	83			
2	0 102	36	44	250	0 103	38	64	60		
2 1/4	0 100	21	35		0 096	48	72			
2 1/2	0 098	+++	+++	250	0 102	+++	+++	60		
2 3/4	0 093	+	++		0 100	+	+			
3	0 100	+	++		0 100	—	+			
3 1/4	0 098	+	+		0 103	—	+			
3 1/2	0 098	—	±		0 107	—	+			
3 3/4	0 108	—	—		0 108	—	+			
4	0 107	—	—		0 107	—	+			

TABLE 13—Results of the Analyses of the Contents of the Stomach and the Duodenum Following the Intraduodenal Injection of 20 Per Cent Dextrose in the Amount of 1 Gm Per Kilogram of Body Weight in a Man, Aged 21, Weighing 47.7 Kg, Who Had Diabetes Mellitus

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice			Duodenal Return					
		Free HCl	Total Acidity	Amount of Juice, Cc	Amount of Juice, Cc	Trypsin Kilo-Units (Amount × Activity)	Amylase Kilo-Units (Amount × Activity)	Lipase Kilo-Units (Amount × Activity)	Bile Pigment (Dilution × Amount)	Bile Acids (Dilution × Amount)
Fasting										
1/4	0 234	17	32	5 0						
1/2		42	55	5 6	21 0	4,200	26,670	4,704	231	8,400
3/4		29	43	6 6						
1	0 236	38	50	5 7	16 0	8,000	39,648	4,320	640	17,600
Following an injection of dextrose										
1/4	0 245	0	6	17 8						
1/2	0 296	0	4	36 0	11 5	3,680	15,859	5,865	4,025	11,500
3/4	0 291	0	2	10 8						
1	0 331	0	±	13 0	77 0	15,400	96,558	31,416	1,848	53,900
1 1/4	0 292	0	±	0 3						
1 1/2	0 257	0	±	0 6	13 4	4,288	15,316	4,824	804	34,840
1 3/4	0 238	0	±	0 6						
2	0 236	0	±	0 6	1 0	200	1,704	435	20	700
2 1/4	0 234	0	±	0 4						
2 1/2	0 221	0	±	0 3	1 8	225	643	252	2	144
2 3/4	0 221	0	±	Trace						
3	0 190	0	+	0 2	5 0	400	1,720	440	5	500
3 1/4	0 190	0	+	Trace						
3 1/2	0 168	22	36	2 5	1 2	60	402	132	1	96
3 3/4	0 189	25	40	3 2						
4	0 154	30	55	3 0	5 2	1,040	8,419	1,716	182	6,240

whether it plays its destined rôle in some compensated manner. We made experiments on diabetic patients with a high level of blood sugar in the same way as we did on normal subjects, namely, by introducing grape sugar to produce hyperglycemia and hypoglycemia. We found also that, in diabetes, in fasting, the secretion of pancreatic and biliary juices was abundant and the acidity of the gastric juice high (for example, free hydrochloric acid 42, total acidity 55, pepsin 200 units), although the blood sugar content was 0.234 and 0.236 per cent, a value much higher than we obtained as the maximal value by

TABLE 14—*Results of the Analyses of the Gastric\* and the Duodenal Contents Following the Intravenous Injection of 25 Per Cent Dextrose in the Proportion of 1 Gm Per Kilogram of Body Weight in a Man, Aged 31, with Diabetes Mellitus*

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Amount of Juice, Cc	Duodenal Return				
			Trypsin Kilo-Units (Amount × Activity)	Amylase Kilo-Units (Amount × Activity)	Lipase Kilo-Units (Amount × Activity)	Bile Pigment (Dilution × Amount)	Bile Acids (Dilution × Amount)
Fasting							
1½	0.304	22.0	2,200	27,236	10,120	22	2,200
1	0.300	17.5	5,600	26,898	10,500	158	6,125
Following an injection of dextrose							
¼	0.650						
½	0.617	1.2	60	1,802	444	2	180
¾	0.587						
1	0.545	0	0	0	0	0	0
1¼	0.480						
1½	0.465	11.8	0	6,102	3,694	0	0
1¾	0.433						
2	0.414	12.0	0	7,680	5,160	0	0
2¼	0.410						
2½	0.407	11.0	0	7,348	473	0	220
2¾	0.377						
3	0.367	22.0	0	15,114	8,140	0	1,100
3¼	0.355						
3½	0.338	9.0	7,200	27,630	14,580	945	12,600
3¾	0.366						
4	0.343	8.4	1,680	22,579	7,006	34	2,520

\* All fractions of gastric juice remained alkaline during the course of the experiment.

introducing grape sugar in the amount of 1 Gm per kilogram of body weight into the duodenum in normal cases. By introducing the same amount of sugar in diabetes, however, we found that the gastric juice became promptly achlohydric and the secretion of pancreatic and biliary juices gradually became scant. Following the hyperglycemia (in which the highest level reached by the blood sugar was 0.331 per cent), a relative hypoglycemia (in which the lowest level reached was 0.154 per cent in four hours in the same case) occurred, and a gastric secretion of fairly high acidity (free hydrochloric acid 40, total acidity 55, pepsin 250 units) followed, accompanied by pancreatic and biliary secretion. From these observations, it is obvious that the humoroneural regulation also plays a part in diabetes mellitus, only the entrance of the excitatory

TABLE 15—Results of the Analyses of the Duodenal Contents in a Youth, Aged 19, Weighing 55 Kg A, Following an Intraduodenal Injection of 0.2 Per Cent Hydrochloric Acid, 100 Cc

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Amount of Juice, Cc	Duodenal Return				
			Trypsin Kilo-Units (Amount × Activity)	Amylase Kilo-Units (Amount × Activity)	Lipase Kilo-Units (Amount × Activity)	Bile Pigment (Dilution × Amount)	Bile Acids (Dilution × Amount)
Fasting ½	0.100	19.3	3,860	31,247	9,071	386	13,510
Following an injection of hydrochloric acid ½	0.098	92.0	14,720	67,732	45,264	11,880	340,600
1	0.107	40.0	8,000	56,760	23,040	1,360	40,000
1½	0.105	31.0	9,920	54,002	15,810	1,240	37,200
2	0.107	46.5	9,300	89,420	20,460	1,023	32,550
2½	0.109	22.5	4,500	48,083	5,445	23	1,688
3	0.107	32.5	10,400	83,785	14,625	1,105	32,500
3½	0.097	28.0	14,000	69,272	12,600	2,600	98,000
4	0.095	36.0	11,520	51,084	27,540	1,728	61,200

*B, Following the Intraduodenal Injection of 20 Per Cent Dextrose in the Amount of 1 Gm Per Kilogram of Body Weight and 0.2 Per Cent Hydrochloric Acid, 100 Cc*

Fasting ½	0.111	35.0	17,500	98,105	6,510	2,660	59,500
1	0.106	32.0	10,240	77,600	5,760	1,920	38,400
Following an injection of dextrose ¼	0.148						
½	0.157	56.0	11,200	35,896	45,920	7,280	252,000
Following an injection of hydrochloric acid ¾	0.145						
1	0.114	52.0	1,040	12,320	5,096	0	104
1¼	0.095						
1½	0.101	7.4	222	6,586	370	0	15
1¾	0.099						
2	0.097	33.5	1,065	69,781	1,675	0	67
2¼	0.102						
2½	0.104	48.0	8,480	122,928	12,288	0	96
2¾	0.102						
3	0.100	30.5	7,625	58,316	5,948	61	1,525
3¼	0.102						
3½	0.104	23.0	4,600	47,361	8,280	69	1,150
3¾	0.100						
4	0.099	39.0	12,480	73,671	25,155	702	19,500

*C, Following the Intravenous Injection of 25 Per Cent Dextrose in the Proportion of 1 Gm Per Kilogram of Body Weight and the Intraduodenal Injection of 0.2 Per Cent Hydrochloric Acid, 100 Cc*

Fasting ½	0.104	13.8	4,416	26,248	11,592	718	10,350
1	0.100	50.0	16,000	100,100	87,000	2,100	35,000
Following an injection of dextrose ¼	0.359						
½	0.309	10.4	5,200	23,639	2,040	1,144	16,640
Following an injection of hydrochloric acid ¾	0.220						
1	0.166	70.0	7,000	52,570	23,800	2,590	35,000
1¼	0.121						
1½	0.090	39.0	12,480	51,051	31,590	2,535	46,800
1¾	0.068						
2	0.075	66.0	33,000	150,084	42,900	7,590	112,200
2¼	0.095						
2½	0.093	88.0	44,000	161,392	127,600	12,320	264,000
2¾	0.095						
3	0.091	62.0	31,000	140,988	77,500	6,200	105,400
3¼	0.093						
3½	0.095	37.5	18,750	91,200	20,250	2,250	46,875
3¾	0.097						
4	0.100	62.0	31,000	128,712	35,650	3,844	77,500

or the inhibitory impulse to the secretory centum being different from that in normal cases. The blood sugar content of 0.154 per cent is the highest value that we obtained by introducing sugar into the duodenum in the amount of 1 Gm per kilogram of body weight in normal cases, a value which in diabetes mellitus induced the secretion of digestive juices as the hypoglycemic reaction. From these results, it is also evident that the process of the hypoglycemic and hyperglycemic alternation itself stimulates the excitatory and the inhibitory functions of the secretory centum and not their durable state, which perhaps causes an accommodation such that stimulation is not any longer induced.

TABLE 16—*Results of the Analyses of the Pancreatic Juice of a Male Dog, Weighing 14.5 Kg, Which Was Provided with a Pancreatic Fistula Under Morphine Anesthesia, and Which Received an Intraduodenal Injection of 0.4 Per Cent Hydrochloric Acid and an Intravenous Injection of 25 Per Cent Dextrose, 100 Cc*

Times at Which Specimens Were Collected, Minutes	Blood Sugar, per Cent	Pancreatic Juice						
		Trypsin			Amylase		Lipase	
		Amount, Cc	Activity Units	Efficiency Units	Activity Units	Efficiency Units	Activity Units	Efficiency Units
Fasting	0.129							
Following an injection of hydrochloric acid, 20 cc								
10	0.113							
20	0.124							
30	0.112	0.5	1,250	625	4,470	2,235	2,600	1,300
Following an injection of dextrose								
15	0.389							
25	0.327							
Following an injection of hydrochloric acid, 20 cc (30 minutes after an injection of dextrose)								
5	0.260							
15	0.234							
25	0.197							
30		1.1	800	880	4,075	4,483	650	715
90	0.106							
Following an injection of hydrochloric acid								
10	0.115							
30		1.1	800	880	4,075	4,483	820	902

#### THE HUMORONEURAL REGULATION AND THE HUMORAL MECHANISM

As previously noted, the classic experiments of Bayliss and Starling showed that with the action of dilute acid on the duodenal mucosa, a substance, secretin, is formed, which can accelerate the pancreatic secretion even when all nervous connections with the secretory gland are severed. An important question arose, therefore, as to how these two mechanisms, the humoroneural regulation and the humoral mechanism, play parts without interference with each other under normal conditions. As has been mentioned, we found that, at the stage of complete cessation of the secretion on administration of dextrose by way

TABLE 17—*Results of the Analyses of the Pancreatic Juice of a Male Dog, Weighing 16 Kg, Which Was Provided with a Pancreatic Fistula Under Morphine Anesthesia, and Which Received Intravenous (V Jugularis) Injections of Vasodilatin-Free New Secretin and of 25 Per Cent Dextrose (V Saphena), 150 Cc*

Times at Which Specimens Were Collected, Minutes	Blood Sugar, per Cent	Pancreatic Juice						
		Amount, Cc	Trypsin		Amylase		Lipase	
			Activity Units	Efficiency Units	Activity Units	Efficiency Units	Activity Units	Efficiency Units
Fasting	0.143							
Following an injection of secretin, 10 cc								
10	0.145	7.2	500	3,600	1,459	10,505	450	3,240
20	0.145	2.3	500	1,150	1,119	2,574	320	736
30	0.139	0.2						
Following an injection of dextrose								
15	0.411							
30	0.392							
Following an injection of secretin,* 10 cc								
10	0.385	7.0	500	3,500	1,459	10,213	290	2,030
20	0.362	2.9	320	928	941	2,729	310	899
30	0.332	0.4						
105	0.254							
Following an injection of secretin,* 10 cc								
10	0.250	4.5	500	2,250	1,119	5,036	270	1,215
20	0.218	1.8	320	576	402	724	230	414
30	0.210	0.2						

\* The interval between the first and the second injections of secretin was one hour and twenty five minutes and that between the second and the third was also one hour and twenty five minutes

TABLE 18—*Results of the Analyses of the Pancreatic Juice of a Dog, Weighing 10.5 Kg, Which Was Provided with a Permanent Pancreatic Fistula (Without Anesthesia), and Which Received Intravenous Injections of Vasodilatin-Free Secretin and of 25 Per Cent Dextrose, 100 Cc*

Times at Which Specimens Were Collected, Minutes	Blood Sugar, per Cent	Pancreatic Juice						
		Amount, Cc	Trypsin		Amylase		Lipase	
			Activity Units	Efficiency Units	Activity Units	Efficiency Units	Activity Units	Efficiency Units
Fasting	0.102							
Following an injection of secretin, 10 cc								
10	0.104							
30	0.104	1.1	500	550	3,226	3,549	1,080	1,183
1 hour	0.099	0.3						
2 hours	0.103							
Following an injection of dextrose								
10	0.366							
20	0.301	No secretion						
Following an injection of secretin 10 cc								
10	0.214							
20	0.177							
1 hour	0.129	0.3						
30	0.141	1.0	500	500	3,226	3,226	1,020	1,020



of the duodenum, an injection of hydrochloric acid (100 cc of a 0.2 per cent solution) caused but little secretion of pancreatic juice and bile. This was particularly so when a marked evacuation of the gall and the pancreatic tracts, including the gallbladder, had occurred previously through the introduction of dextrose solution into the duodenum, whereas, when the hyperglycemia was induced by intravenous administration of dextrose, an abundant fluid was obtained by the injection of hydrochloric acid into the duodenum, as in the case of fasting. This fluid was extremely rich in bile pigment and poor in enzymatic activity, so that it must have been mainly the consequence of the

TABLE 19—*Results of the Analyses of the Gastric Juice from a Youth, Aged 19, Following Subcutaneous Injections of Histamine, 1 Mg, with and without a Simultaneous Intraduodenal Injection of 25 Per Cent Dextrose in the Amount of 1 Gm Per Kilogram of Body Weight*

Times at Which Specimens Were Collected, Hours	With an Injection of Dextrose				Without an Injection of Dextrose			
	Blood Sugar, per Cent	Gastric Juice			Blood Sugar, per Cent	Gastric Juice		
		Free HCl	Total Acidity	Amount of Juice, Cc		Free HCl	Total Acidity	Amount of Juice, Cc
<b>Fasting</b>								
1/4	0.097	0	13	3.0	0.095	0	10	8.8
1/2		13	21	3.4		3	15	7.8
3/4		17	30	0.8		0	7	8.6
1	0.095	23	34	12.0	0.099	0	7	2.5
<b>Following injections of histamine and dextrose</b>					<b>Following an injection of histamine</b>			
1/4	0.150	43	50	1.3	0.102	30	42	17.5
1/2	0.165	46	54	14.5	0.096	74	80	39.0
3/4	0.144	40	52	54.5	0.099	38	46	24.0
1	0.100	18	27	19.0	0.095	23	33	9.8
1 1/4	0.071	2	11	5.8		16	25	10.0
1 1/2	0.080	0	8	9.3	0.100	23	30	15.5
1 3/4	0.087	0	10	12.5		34	42	12.5
2	0.095	18	27	4.0	0.100	35	41	8.2
2 1/4	0.089	32	48	6.5		18	23	4.0
2 1/2	0.093	0		5.0	0.102	23	29	1.8
2 3/4	0.093	0		4.3		22	29	1.5
3	0.091	0		5.8	0.088	0	0	0

reflex evacuation of the gall tracts, including the gallbladder. From this result, it is evident that the hydrochloric acid solution, when introduced into the duodenum, causes a reflex gush of the duodenal return as other solutions, the hydrochloric acid seeming to make up the main part of the collected juice, though the return may be effected partly also by the secretin mechanism. Therefore, from this experiment, we were not able to decide whether the humoroneural regulation has any influence on the secretin mechanism or not. It was shown in the first paper that a dog anesthetized with morphine and provided with a pancreatic fistula does not show this reflex mechanism, so that an injection of alcohol or ether into the duodenum does not cause any secretion of the pancreatic juice, but an injection of hydrochloric acid causes an abundant secretion of that as the effect of the secretin mechanism. We therefore tried the same experiment before and after an intravenous injection of dextrose

An injection of 20 cc of 0.4 per cent hydrochloric acid thirty minutes after the intravenous injection of 100 cc of 25 per cent dextrose caused just as abundant a secretion of pancreatic juice as when an injection of dextrose was not made or as when the hyperglycemic period after the administration of dextrose was over. From this result, it is obvious that the humoneural regulation does not interfere with the humoral mechanism. To show this more exactly, we prepared the vasodilatin-free new secretin after the procedure of Weaver, Luckhardt and Koch<sup>43</sup> and injected this intravenously in the normoglycemic and in the hyperglycemic periods. Also, it was possible that anesthesia had some influence on the neural component of the humoneural regulation, a dog with a permanent pancreatic fistula was used, and secretin was injected before and after the administration of dextrose, without anesthetics being used. All the results coincided with that obtained by intraduodenal injection of hydrochloric acid. Normally, however, during the stage of hyperglycemia, gastric secretion does not occur, even when foods are ingested and acid chyme is not poured into the duodenum, so that it fails to show the activity of the secretin mechanism at this period.

Histamine is known as a strong humoral excitant of the gastric secretion. Therefore, we injected this substance during periods of fasting, as well as at the stage of hyperglycemia. A profuse secretion of gastric juice with high acidity also occurred at the stage of hyperglycemia on the injection of histamine.

From these observations, we may conclude that the humoneural regulation and the humoral mechanism play parts without interference one with the other and that at the stage of inhibition by hyperglycemia there is no occasion for the humoral mechanism to function. On the other hand, it is proved that the pancreatic secretion is not necessarily disturbed by disturbed gastric secretion, a fact that tells us that the humoneural regulation alone, without the cooperation of the secretin mechanism, is sufficient to excite the secretory glands of the pancreas to activity.

#### COMMENT

The conclusion from the results obtained is, in short, that hyperglycemia inhibits the secretions of the digestive juices, and hypoglycemia accelerates it. The process of the inhibitory impulse and of the excitatory impulse is first evoked humorally at the secretory centrum and from this is transmitted through the autonomic nervous system to the acting tissue cells. Incretions, extracts of tissue, foods, medicaments and the like that are apt to cause hyperglycemia have, in general, an

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<sup>43</sup> Weaver, M. M., Luckhardt, A. B., and Koch, F. C. Vasodilatin-Free Pancreatic Secretin, *J. A. M. A.* **87**: 640 (Aug. 28) 1926.

inhibitory influence on the secretion of the digestive juices, while those that tend to produce hypoglycemia have an excitatory action. The regulatory mechanism seems to function with great precision. There have been many reports that hypertonic solutions, in general, have an inhibitory influence on the secretion of the digestive juices, sugar having the most significant effect. A remarkable survey in this connection was made by Karmel,<sup>44</sup> together with the report of his own experiments. On careful inspection, however, this is seen to refer rather to the quantities of the substances administered than to the concentrations of them, as comparison is usually made with the results obtained in using different concentrations and the same volumes of the solutions. In the present study, we found that dextrose had quite the same inhibitory effect on the secretion of digestive juices in isotonic or somewhat hypotonic solutions as in hypertonic solutions, if the quantity is sufficient. In diabetes mellitus, a condition that shows hyperglycemia even at a time of fasting, the same inhibitory and excitatory mechanism is in force, being different from that in normal cases only in the manner of entrance of these impulses. It is evident from this that the process of the hypoglycemic and hyperglycemic alternation stimulates the excitatory and the inhibitory functions of the secretory centrum and that the latter is not stimulated by the durable state of them, which, perhaps, causes an accommodation such that stimulation is not any longer induced. A rush of dextrose into the circulatory system gives rise to an impulse inhibitory of the secretions of the digestive juices, as well as of motility, so that there is a "full feeling." The effect of this is that the subject refuses foods, and if foods are administered, a direct secretion of gastric juice does not occur and acid chyme is not poured into the duodenum. When hypoglycemia occurs, there develops an excitatory impulse of the secretory function, as well as of motility, so that there is a feeling of hunger. This causes the subject to take foods eagerly, and the digestion and resorption occur promptly to meet the needs. On the basis of these observations, we advanced the theory of the "humoroneural regulation of the secretion of digestive juices." The relation of this regulation to the humoral mechanism was also studied, and the results indicated that both mechanisms play their parts without interference one with the other. When hyperglycemia develops, the gastric secretion ceases and the entrance of the acid chyme into the duodenum also ceases, so that the secretin mechanism does not have any occasion to function during this period. A hypoglycemia causes a profuse secretion of gastric juice and a gush of abundant acid chyme into the duodenum, which, in turn, induces a full functioning of the secretin

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44 Karmel J. Ueber den Einfluss intravenos verabreichter hypertonomischer Lösungen auf die Magensekretion, *Wien klin Wchnschr* **35** 1007, 1922

mechanism When, however, there is a disturbance of the gastric secretion, as in achylia gastrica and cancer of the stomach, the humoroneural regulation alone, without the cooperation of the secretin mechanism, is sufficient to excite the secretory glands of the pancreas to activity Histamine, a substance highly potent humorally for the excitation of the secretion of the gastric juice, causes a profuse secretion of this even at the point of hyperglycemia This fact indicates that the humoroneural regulation does not have any remarkable influence on the humoral mechanism, and this, in turn, indicates that the action of histamine does not have anything to do with the neural mechanism There exists also a purely neural (reflex) mechanism of the gastric, pancreatic and biliary secretions, the interrelation of which to the humoroneural and the humoral mechanism will be discussed at another occasion

#### SUMMARY

1 Insulin provokes gastric, pancreatic and biliary secretion, and epinephrine inhibits it (only the influence of epinephrine on the gastric secretion is not so decisive) Ephedrine has an effect similar to that of epinephrine The increased secretion of these juices after the injection of insulin is marked in the presence of a pronounced hypoglycemia, while it is nearly negative in the absence of hypoglycemia The decrease of the secretion of these juices after the injection of epinephrine goes parallel with hyperglycemia, and is followed by an increase of secretion when a reactive hypoglycemia occurs

2 Also in cases of cancer of the stomach, in which the gastric juice remained alkaline during the course of the collection, a marked increase of the secretion of pancreatic and biliary juices after the injection of insulin was observed, indicating that insulin primarily stimulates the secretion of these juices

3 The increased secretion of gastric and pancreatic juices and of bile induced by the injection of insulin is almost completely inhibited by an injection of dextrose, but a profuse secretion again occurs when hypoglycemia recurs Therefore, it is definitely shown that hypoglycemia, if it does not alone stimulate the secretion of these juices, does so when insulin is injected

4 An injection of atropine causes a distinct inhibition of the increased secretion of these juices induced by the injection of insulin, indicating that hypoglycemia exerts its stimulating effect on the centrum of the secretory nerve and that the stimulus is transmitted to the acting tissue cells through the parasympathetic nervous system

5 When dextrose is introduced into the duodenum, it usually brings about an initial increase of the secretion of pancreatic juice and of bile, perhaps as a reflex evacuation of the gall and pancreatic tracts, including

the gallbladder. Hyperglycemia, after resorption of the dextrose, however, stops the secretion of pancreatic and biliary juices almost entirely, and the gastric content becomes achlorhydric. Following the hyperglycemia, a reactive hypoglycemia is evoked which is accompanied by a profuse secretion of digestive juices. An intravenous injection of dextrose has almost the same effect, except that the initial increase usually does not occur and the diminution of the gastric secretion is manifested in amount rather than in acidity. An isotonic or rather a somewhat hypotonic solution of dextrose has the same inhibitory influence on the secretion of the digestive juices as a hypertonic solution, if the amount is sufficient. Therefore, it is definitely proved that hypoglycemia, in general, stimulates the secretory nervous centrum and hyperglycemia inhibits it and that the stimulus is transmitted through the parasympathetic nervous system to the reacting tissue cells, while the inhibitory impulse most likely is transmitted through the sympathetic nervous system.

6 The test breakfast does not cause any secretion of acid or causes a markedly diminished secretion of acid by the stomach at the stage of hyperglycemia, in comparison with its effect on the secretion of acid at a time of fasting. The motility of the stomach is also inhibited, so that the bread remnants of the test meal are detectable for a much longer time by fractional suction. Hypoglycemia is accompanied usually by hunger, and hyperglycemia by a "full feeling."

7 Since hypoglycemia induces a humorally excitatory impulse and hyperglycemia an inhibitory impulse to the secretory centrum and since from this centrum the stimulus and the inhibitory impulse are transmitted through the autonomic nervous system to the acting tissue cells, this process might be called the "humoroneural regulation of the secretion of the digestive juices." The secretion of saliva is excepted from this regulation.

8 In diabetes mellitus, the same inhibitory and excitatory mechanism is also in force, being different from that in normal cases only in the manner of entrance of these impulses. It is evident from this fact that it is the process of the alternation of hypoglycemia and hyperglycemia that stimulates the excitatory and the inhibitory functions of the secretory centrum and not the durable state of them, which perhaps causes an accommodation such that stimulation is not any longer induced.

9 The humoroneural regulation and the humoral mechanism normally cooperate without interference one with the other, an intravenous injection of secretin causing nearly as abundant a secretion of pancreatic juice at the stage of hyperglycemia as at a time of fasting. When hyperglycemia develops, gastric secretion ceases and the entrance of the acid chyme into the duodenum also ceases, so that the secretin

mechanism does not have any occasion to function during this period. A hypoglycemia causes a profuse secretion of gastric juice and an abundant gush of acid chyme into the duodenum, which, in turn, induces the full functioning of the secretin mechanism. When, however, a disturbance of gastric secretion occurs, as in achylia gastrica and in cancer of the stomach, the humoroneural regulation alone, without the cooperation of the secretin mechanism, excites the secretory glands of the pancreas to activity.

10 Histamine, a vigorous excitant of the gastric secretion humorally, causes also a profuse secretion of gastric juice at the high point of hyperglycemia. Therefore, it follows that the humoroneural regulation does not have any remarkable influence on the humoral mechanism and thus, in turn, proves that the action of histamine does not have anything to do with the neural mechanism.

# THE ANDREWES DIAZO REACTION IN NEPHRITIS\*

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Microchemical examinations of the blood are being more and more utilized as aids in the rational diagnosis, prognosis and treatment of disease. Probably no other disease offers as great a variety of chemical changes as that involving cases of renal insufficiency with concomitant retention of many of the urinary constituents. Among these compounds are such familiar chemical entities as urea, creatinine, uric acid, phosphorus and other substances, the variations and clinical significances of which are well known. Circulating in the blood stream, however, are a considerable number of unexamined or ill defined substances awaiting identification and clinical evaluation.

In 1924, while working on the van den Bergh reaction, C H Andrewes discovered a new diazo color reaction which seemed to be given only by uremic serums<sup>1</sup>. The diazo reagent, diazobenzene sulphonic acid, is a familiar laboratory reagent which has been found to couple with a variety of substances yielding variously colored solutions. Ehrlich<sup>2</sup> was probably the first to use the diazo reaction in clinical medicine. He applied the test to urine and found it of special significance in the treatment of patients with typhoid fever, measles, certain types of tuberculosis and other disorders. Hunter<sup>3</sup> used the reaction in his attempt to systematize the different types of diazo reaction in normal and pathologic urines, while Koessler and Hanke<sup>4</sup> utilized it extensively in their work on the proteinogenous amines and in their studies on intestinal putrefaction. Van den Bergh,<sup>5</sup> McNee<sup>6</sup> and others<sup>7</sup> employed the reaction in their studies on serum bilirubin to

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1 Andrewes, C H. *Lancet* **1** 590, 1924

2 Ehrlich, P. *Ztschr f klin Med* **5** 285, 1882

3 Hunter, G. *Biochem J* **19** 25, 1925

4 Koessler, K K, and Hanke, M T. *J Biol Chem* **39** 507, 1919, **50** 237, 1922, **59** 837, 839 and 901, 1924

5 Van den Bergh, A A H. *Der Gallenfarbstoff im Blute*, Leiden, 1919

6 McNee, J W. *Quart J Med* **16** 390, 1923

7 Green, C H, and Conner, H M. *Diseases of the Liver. Comparative Study of Tests for Hepatic Function in Certain Diseases of the Hematopoietic System*, *Arch Int Med* **38** 167 (Aug) 1926

distinguish certain types of jaundice, while Davies and Dodds<sup>8</sup> have studied the properties of pure bilirubin and its behavior toward the diazo reagent

Andrewes noticed, on the addition of the diazo reagent (diazotized sulphanilic acid) to an alcoholic extract of uremic serum, the appearance of a buff coloration in the course of an hour or two, whereas normal serum under similar experimental conditions gave little, if any, color. He found that it was necessary to allow the reaction mixture to stand at room temperature for about twenty-four hours in order to obtain the maximum color development. After the buff color had appeared, the addition of a few drops of strong sodium hydroxide produced a bright cherry red, whereas normal serum yielded neither the buff nor the red colorations. Although the buff tint was rather permanent, the red color was somewhat fleeting and lasted from a few seconds to a half hour or more, depending on the concentration of the unknown substance in the original serum. C. H. Andrewes found that a positive reaction was given only by patients with severe uremia who had a blood urea of 220 mg or more per hundred cubic centimeters of blood. A positive test did not seem to be associated with twitchings or convulsions and seemed to occur in any of the clinical types of uremia. In two cases in which the serum gave a positive reaction, the cerebrospinal fluid yielded a negative reaction. In regard to one serum, which gave a strong positive test, the corresponding cerebrospinal fluid, which was practically uncontaminated with blood, gave a faint buff coloration which turned pink on alkalization. Three rabbits with a high blood urea content, two of which had experimental nephritis, gave negative reactions. Hewitt<sup>9</sup> confirmed the observations of Andrewes in regard to the diazo reaction of uremic serum and has introduced an important simplification of the test. Instead of allowing the reacting mixture to stand for twenty-four hours, Hewitt found that the maximum buff coloration could be developed by boiling the solution for thirty seconds, on the addition of the alkali the cherry-red color appeared as usual. Whereas Andrewes reported that normal urine gave a negative diazo reaction, Hewitt found that alcoholic extracts of urine, under these experimental conditions, sometimes gave a diazo reaction similar to that given by uremic serum. Hewitt suggested that the reaction might be attributed to a cyclic amine such as tyramine or histamine. In a later paper, Harrison and Hewitt<sup>10</sup> stated that they had obtained a clue as to the nature of the substance responsible for the reaction and

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8 Davies, D. T., and Dodds, E. C. *Brit J Exper Path* **8** 316, 1927

9 Hewitt, L. F. *Biochem J* **19** 171, 1925

10 Harrison, G. A., and Hewitt, L. F. *Brit M J* **2** 1138, 1927



that the substance is certainly present in normal urine. Hunter and Montgomery<sup>11</sup> also found that normal urine gives a positive test, whereas normal feces does not. More recently, Harrison and Bromfield<sup>12</sup> concluded that the substance responsible for the Andrewes reaction is an indoxyl compound, presumably potassium indoxyl sulphate (indican) or possibly in part indoxyl glucuronate.

In Canada, Rabinowitch,<sup>13</sup> studying the Andrewes diazo test, reported that a positive test was found only in blood from patients showing marked retention of waste products with lesions such as advanced chronic nephritis, acute surgical conditions of the kidneys, pyonephritis and similar conditions. He stated "in view of the positive reactions invariably noted in definite uremics, and the negative reactions in the subjects with obviously predominant arterial disease, the negative reactions noted in the few cases with suggested uremic symptoms appear to have some diagnostic significance." He suggested that a positive diazo test may have a greater prognostic significance, as regards time factor, than the blood creatinine in chronic nephritis. Blotner and Fitz<sup>14</sup> utilized the reaction and found it of considerable diagnostic value. They decided that a high blood urea content accompanied by a positive diazo reaction was more significant than when it was accompanied by a negative reaction. They found that the ascitic fluid of one patient gave a positive test, whereas the cerebrospinal fluid did not. Two rabbits and one dog on which nephrectomy had been performed gave positive diazo tests one or two days after removal of the kidneys. Davis<sup>15</sup> reported three cases of chronic nephritis with positive diazo reactions. In his work on experimental uremia, Edmund Andrews<sup>16</sup> concluded that "if animals in which suppression of urine is brought about by either nephrectomy or acidosis are injected with hypertonic salt solution in amounts such that chloride content of the blood is comparable to that in uremia, they pass into a condition resembling uremia. Every manifestation of uremia seen in the human being is reproduced. This is true of the histologic and chemical factors as well." He found that, while his control animals on which nephrectomy had been performed gave negative diazo reactions throughout, those that received injections of hypertonic saline solutions gave positive reactions within a short time. On the other hand,

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11 Hunter, G., and Montgomery, R. C. *Canad. M. A. J.* **17** 1448, 1927.

12 Harrison, G. A., and Bromfield, R. J. *Biochem. J.* **22** 43, 1928.

13 Rabinowitch, L. M. *Canad. M. A. J.* **15** 725, 1925.

14 Blotner, H., and Fitz, R. *Diazo Test in Nephritis*, *J. A. M. A.* **88** 985 (March 26) 1927.

15 Davis, Jr., W. J. N. *U. S. Nav. M. Bull.* **26** 105, 1928.

16 Andrews, Edmund. *Experimental Uremia*, *Arch. Int. Med.* **40** 548 (Oct) 1927.

Hunter and Montgomery<sup>11</sup> performed nephrectomy on four rabbits and a number of dogs. All of these animals soon developed positive reactions.

Shortly after the work of C. H. Andrewes was published, a diazo and urochromogen reaction in blood filtrates of uræmic serums was announced by Becher.<sup>17</sup> His reaction was carried out in a trichloroacetic acid filtrate of whole blood or serum. His test consisted essentially of a more or less quantitative difference between the color produced by a normal blood filtrate and that given by a filtrate of a uræmic serum, both tests being performed at the same time. Becher made an extended search for the substance responsible for this color reaction. He decided that the aromatic oxyacids, which, in part, are free in the blood, and the oxyprotein fraction are mainly responsible for his diazo reaction. Becher's test is somewhat different from that of Andrewes, and is, therefore, hardly comparable. Hewitt expressed the belief that the substance responsible for the Andrewes diazo reaction is not the same as that which yields the Becher reaction.

#### EXPERIMENTAL WORK

The Andrewes diazo reaction, as modified by Hewitt, is a simple test which can be carried out with little difficulty.

##### Reagents

Solution 1	Sulphanilic acid	1 Gm
	Concentrated hydrochloric acid	15 cc
	Distilled water	to 1,000 cc
Solution 2	Sodium nitrite	0.5 Gm
	Distilled water	to 100 cc

The reagent is prepared by mixing 25 cc of solution 1 with 0.75 cc of solution 2. To one volume of serum or plasma are added two volumes of alcohol, and the precipitated proteins are separated by centrifugating or filtering. One volume of the freshly prepared diazo reagent is added to four volumes of the alcoholic extract, and the mixture is boiled for about one-half minute. At this point, preparations from diazo-positive serums will yield a buff-colored solution, whereas preparations from normal serums will yield colorless or only faintly colored solutions. Then a solution of 40 per cent sodium hydroxide is added drop by drop. The test is positive if a definite pink or cherry-red color results on alkalization. The pink color lasts from a few seconds to an hour or more depending on the concentration of the substance in the original serum.

In view of the fact that we use the Thannhauser and Anderson<sup>18</sup> modification of the van den Bergh method for the routine determination of serum bilirubin, we have found it convenient to use their

17 Becher, E. *Arch f klin Med* **148** 10, 1925.

18 Thannhauser, S. J., and Anderson, E. *Arch f klin Med* **137** 179, 1921.

solutions for the diazo reaction They are, of course, similar to those used by Andrewes and by Hewitt but contain more sulphanilic acid and hydrochloric acid

Solution 1	Sulphanilic acid	5 Gm
	Concentrated hydrochloric acid	50 cc
	Distilled water	to 1,000 cc
Solution 2	Sodium nitrite	0.5 Gm
	Distilled water	to 100 cc

The diazo reagent was prepared by diluting 0.8 cc of freshly prepared nitrite solution to 25 cc with solution 1 To one volume of blood plasma or serum was added two volumes of alcohol and the precipitated proteins separated by centrifugating To 1 cc of the clear alcoholic extract were added 0.5 cc of alcohol and 0.25 cc of the freshly prepared diazo reagent The mixture was boiled for thirty seconds and then 10 per cent sodium hydroxide was added drop by drop until the maximum color change was developed

While this diazo reagent may not be as sensitive to slight traces of the color-producing substance, it seems to produce a more intense cherry red which may persist for an hour or even longer dependent on the amount of substance in the original uremic serum The length of time the color lasts seems to be roughly proportional to the intensity of the color which, in turn, is probably proportional to the concentration of the material in the serum Hence, we have found it convenient to report the positive reactions in terms of the minutes that the pink color persists In that manner, a rough quantitative factor is introduced Those cases in which the color remained less than five minutes are, however, reported as lasting five minutes It was soon observed that the substance responsible for the color reaction was not only permanent in alcoholic solution, but that uremic blood, serum or plasma which had stood several days still yielded a positive reaction When a jaundiced serum or plasma is deproteinized with alcohol and the mixed diazo reagent then added, a pink color soon appears owing to the coupling of the bile pigments with the diazotized sulphanilic acid On the addition of alkali the pink changes to violet or green which may conceal the cherry-red color of a weakly positive diazo test It has been pointed out,<sup>19</sup> however, that a hypobilirubinemia is the rule in nephritis, and we have found that such is the case The other methods used in the experimental work are those in common usage in hospital laboratories The blood urea content was determined by the direct nesslerization method of Karr,<sup>20</sup> creatinine by the method of

19 Feigl, J, and Querner, E *Ztschr f d ges exper Med* 9 153, 1919

20 Karr, W G *J Lab & Clin Med* 9 329, 1924

Folin,<sup>21</sup> the carbon dioxide combining power of the plasma according to van Slyke,<sup>22</sup> phosphorus as directed by Benedict and Theis,<sup>23</sup> etc

During the last year the diazo test has been applied to many of the patients admitted to the Mercy Hospital and those seen in the outpatient department. In table 1 are enumerated the number and character of the cases examined, excluding cases of suspected renal disease in which negative reactions to the diazo tests were obtained. Table 2 contains cases in which definite damage to the kidney exists.

TABLE 1—*Cases, Excluding Those of Renal Pathologic Changes with a Negative Diazo Test*

Type of Case	Number	Type of Case	Number
1 Gastro-Intestinal Tract		4 Gynecologic and Obstetric Conditions	29
Gastric ulcer	7	5 Metabolic Disturbances	
Gastritis	1	Diabetes mellitus	12
Colitis	3	Thyroid dysfunction	5
Appendicitis	19	6 Neurologic Conditions	
Intestinal obstruction	1	Meningitis	3
Chemical poisoning (arsenic, methanol, carbon monoxide)	8	Neurosis	6
Alcoholism (acute and chronic)	12	Hysteria	1
2 Respiratory Tract		Epidemic encephalitis	2
Pneumonia	8	Epilepsy	1
Pleurisy	4	Migraine	2
Abscess of the lung	4	Multiple sclerosis	1
Bronchitis	3	Spasmodic torticollis	1
La grip	4	Tetanus	1
Influenza	2	7 Genito Urinary Conditions	7
Empyema	1	8 Minor Surgical Conditions	38
Tuberculosis (pleural and pulmonary)	5	9 Miscellaneous Conditions	
3 Cardiovascular Diseases		Syphilis (various types)	13
Rheumatic cardiovascular disease	7	Neoplasms (benign and malignant)	15
Syphilitic cardiovascular disease	2	Gallbladder disease	10
Arteriosclerotic cardiovascular disease	23	Congenital hemolytic jaundice	1
Hypertensive cardiovascular disease	4	Cirrhosis of liver	2
Hypertension (essential and paroxysmal)	5	Infectious arthritis	5
Hypotension	1	Burns	1
Aneurysm of aorta	1	Hernia	10
Neurocirculatory asthenia	5	Retinitis pigmentosa	1
Cerebral accidents	5	Leukemia (lymphatic)	1
		Morphine addiction	1
Total number of cases		10 Outpatient Department Cases	164
			468

and in which positive diazo reactions might frequently be suspected but in which these reactions were negative. Table 3 includes those cases in which a positive diazo test was obtained.

#### COMMENT

In discussing the various conditions involving the kidneys, a more or less common classification must be used. In this work a slight

21 Folin, O. Laboratory Manual of Biological Chemistry, ed. 3, New York, D. Appleton & Company, 1923.

22 Van Slyke, D. D., and Cullen, G. E. J. Biol. Chem. **30**, 289 and 347, 1917.

23 Benedict, S. R., and Theis, R. C. J. Biol. Chem. **61**, 63, 1924.

TABLE 2—Cases with Renal Pathologic Changes and a Negative Diazo Test

Case	Age	Blood				Urine				Diagnosis	End Result	
		Chemistry				Phenol sulphon phthalein, per Cent	Microscopic					
		Pressure, Mm	Mercury	Urea, Mg	Diazotization, Mg		Cells	Casts				
									Red			White
1	69	296/170	166	2.2	—	1.010	++	+++	++	+	Arteriosclerotic cardiovascular disease, mitral insufficiency, arteriolar nephritis	Improved
2	37	296/170	21	1.5	—	1.018		+	+	+	Chronic diffuse glomerulonephritis, obesity	Improved
3	53	190/80	28		—	1.016		+	++		Chronic arteriolar nephritis, hypertensive cardiovascular disease, infectious arthritis	Improved
4	56	190/95	71	1.8	—	1.023		+	+	+	Chronic nephritis, diabetes mellitus, bronchopneumonia	Died
5	63	98/80	142	2.2	—	1.030		+	+	+	Arteriosclerotic cardiovascular disease, arteriolar nephritis, pneumonia	Died
6			101	1.4	—	1.018		+			Arteriosclerotic cardiovascular disease, arteriolar nephritis, pneumonia	Improved
7	26	120/80	100	1.3	—	1.017	++	+			Acute focal glomerular nephritis, secondary anemia	Improved
8	54	145/75	25	1.5	—	1.017					Chronic arteriolar nephritis, arteriosclerotic cardiovascular disease, pulmonary tuberculosis	Died
9	37	110/90	11	1.1	—	1.015		+	+	+	Pyonephrosis, renal calculus	Improved
10	53	200/126	64	1.6	—	1.029	+	+	+	++	Acute glomerular nephritis	Improved
11	48	181/126	81	1.7	—	1.014			+	+	Arteriolar nephritis, arteriosclerosis with hypertension, coronary sclerosis, cardiac decompensation	Died
12	66	210/150	40	2.9	—	1.024	+	+	+	+	Arteriosclerosis with hypertension, chronic arteriolar nephritis, cystitis	Improved
13	54	166/100	54	1.3	—	1.005		+	+		Chronic glomerular nephritis	Improved
14	65	148/98	46		—	1.009				+	Arteriosclerosis with hypertension, chronic arteriolar nephritis	Improved
15	63	174/70	27	1.3	—	1.021			+		Chronic arteriolar nephritis, pyonephrosis, diabetes mellitus	Died
16	70	150/80	58		—	1.018		+	+	+	Arteriosclerotic cardiovascular disease with auricular fibrillation, chronic myocarditis	Died
17	77	186/120	233	4.6	—	1.010				+	Benign hypertrophy of prostate with obstruction	Improved
18	77	120/66	60	1.8	—	1.017				+	Chronic glomerular nephritis	Improved
19	70	130/81	212	5.2	—	1.010			+		Arteriosclerotic cardiovascular disease with hypertension, chronic arteriolar nephritis	Died
20	70	148/76	38	1.7	—	1.012			+	+	Arteriosclerotic cardiovascular disease, arteriolar nephritis, alcoholism	Improved
21	62	271/130	101	2.8	—	1.012	++	+		+	Arteriosclerosis with hypertension, chronic arteriolar nephritis	Improved
22	58	110/70	129	1.9	—	1.020		+	+	+	Arteriosclerotic cardiovascular disease, chronic arteriolar nephritis, hypertension	Improved
23	60	160/80	49	1.2	—	1.020				+	Arteriosclerotic cardiovascular disease, carcinoma of bladder	Died
24	64	180/90	20		—	1.005		+	+	+		
25	88	180/88	37	1.8	—	1.024	+++	+++	++	+		
26			108		—	1.021						

modification of the clinical pathologic grouping of Volhard and Fahr<sup>24</sup> has been used, which is given in brief

*A* Glomerular nephritis—primary process in the glomeruli

1 Focal

2 Diffuse

(a) Acute, (b) subacute, (c) chronic

*B* Nephrosis—tubular lesion of a degenerative character

1 Kidney of pregnancy

2 Lipoid

3 Amyloid kidney

4 Tubular necrosis, e g, mercuric chloride

*C* Arteriosclerotic diseases of the kidney

1 Renal artery and its larger branches

2 Arterioles

In examining the data it will be seen that the diazo reaction is positive only in those cases in which marked retention of nitrogenous products has taken place. The lowest urea retention which was associated with a positive diazo reaction was 112 mg urea per hundred cubic centimeters of blood, both reactions, of course, being carried out at the same time. Although there is a general parallelism existing between the retention of urea and the substance producing the diazo reaction, there are a number of definite exceptions, as seen in cases 14 and 16 of table 3. In case 14 with a urea value of 245 mg, the pink color of the diazo test lasted for nearly two hours, while in case 16 with a urea of 425 mg the color persisted for only twenty minutes. The highest urea value found associated with a negative diazo test was 293 mg. In other words, a marked nitrogen retention can exist with the diazo test remaining negative as seen in case 15 of table 2.

There does not seem to be any definite relation between the concentration of the blood creatinine and the intensity of the diazo reaction, although a positive test was usually found associated with a definite creatininemia, yet, in a number of cases, creatinine retention was seen with a negative diazo test (cases 12, 15, 17 and 19 of table 2). In regard to case 17, since the creatinine returned so promptly to normal after the obstruction had been relieved, it seems probable that the impairment of renal function was not due to organic change in the kidney. While the data is not given in the tables, the alkaline reserve of the plasma has been determined in a number of cases, and it has been found that those cases with a positive diazo reaction usually showed marked acidosis with a carbon dioxide combining power as

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<sup>24</sup> Volhard, F, Fahr, F, and Elwyn, H. Nephritis, New York, The Macmillan Company, 1926

TABLE 3—Cases with Renal Pathologic Changes and a Positive Diazo Test

Case	Age	Blood			Urine										Final Result
		Pressure, Mm. Mercury	Chemistry			Phenol sulphophthalein, per Cent	Cells			Casts			Diagnosis		
			Urea, Mg	Inulin, Mg	Diazo Reaction		Red	White	Hyaline	Granular	Ulular				
1	40	150/85	325	8.1	30	1.008	+	+	+	+	+	+	Chronic diffuse glomerular nephritis, arteriosclerosis with hypertension	Died	
2	79	130/70	595	0.1	60	1.007	+	+	+	+	+	+	Chronic diffuse glomerular nephritis	Died	
3	32	151/90	211	3.0	5	1.012	+	+	+	+	+	+	Pyelonephritis, cystitis, uremia, paralysis of bladder from injury to the cord	Died	
4	28	116/75	300	3.5	30	1.010	+	+	+	+	+	+	Pyonephrosis, uremia	Died	
5	60	122/82	332	12.0	60	1.010	+	+	+	+	+	+	Arterial nephritis, pericarditis	Died	
6	16	138/60	235	8.8	60	1.015	+	+	+	+	+	+	Arterial nephritis, paresis	Unimproved	
7	21	100/80	181	5.1	5	1.032	+	+	+	+	+	+	Acute nephrosis, bichloride of mercury poisoning	Died	
8	22	110/50	117	3.8	150	1.016	+	+	+	+	+	+	Chronic diffuse glomerular nephritis, uremia	Died	
9	19	110/80	160	6.5	30	1.020	+	+	+	+	+	+	Bilateral pyonephrosis, bronchopneumonia	Died	
10	72	71/50	565	0.0	60	1.010	+	+	+	+	+	+	Hypertrophied prostate, cystitis, arteriosclerosis, arteriolar nephritis, uremia	Died	
11	60	208/80	270	3.2	15	1.010	+	+	+	+	+	+	Arteriosclerotic cardiovascular disease, arteriolar nephritis, cerebral hemorrhage	Died	
12	22	110/85	27	11.0	—	1.012	+	+	+	+	+	+	Acute nephrosis, mercuric chloride poisoning	Died	
13	20	210/150	320	8.1	60	1.012	+	+	+	+	+	+	Chronic diffuse glomerular nephritis, bronchopneumonia	Died	
14	33	160/100	170	2.1	10	1.020	+	+	+	+	+	+	Chronic diffuse glomerular nephritis	Died	
15	55	176/90	105	10.0	60	1.010	+	+	+	+	+	+	Chronic diffuse glomerular nephritis, arteriosclerotic cardiovascular disease	Died	
16	52	130/90	310	8.0	10	1.023	+	+	+	+	+	+	Arteriosclerotic cardiovascular disease, cystitis, urethral stricture	Died	
17	60	130/60	225	8.8	30	1.010	+	+	+	+	+	+	Arteriosclerotic cardiovascular disease	Died	
18	63	160/92	200	5.5	30	1.012	+	+	+	+	+	+	Arterial nephritis, furunculosis	Died	
19	21	90/60	88	2.6	—	1.010	+	+	+	+	+	+	Acute nephrosis, mercuric chloride poisoning	Died	
20	13	130/80	565	10.0	60	1.015	+	+	+	+	+	+	Acute nephrosis, mercuric chloride poisoning	Died	
21	33	203/100	106	6.0	10	1.016	+	+	+	+	+	+	Chronic diffuse glomerular nephritis, uremia	Died	
22	65	95/60	162	5.2	5	1.010	+	+	+	+	+	+	Arteriosclerotic cardiovascular disease, arteriolar nephritis, lobar pneumonia, uremia	Died	
23	45	160/100	215	6.1	+	1.018	+	+	+	+	+	+	Chronic diffuse glomerular nephritis, uremia	Died	
24	13	100/100	600	7.8	90	1.010	+	+	+	+	+	+	Acute nephrosis, mercuric chloride poisoning	Died	
25	20	100/100	100	7.2	60	1.010	+	+	+	+	+	+	Acute nephrosis, mercuric chloride poisoning	Died	

low as 9 per cent by volume. On alkaline therapy, these values were frequently raised temporarily to 30 to 50 per cent. This uræmic acidosis was found to be due primarily to a marked elevation of the inorganic phosphorus content of the blood—values of from 5 to 20 mg of phosphorus per hundred cubic centimeters of serum being obtained in certain cases in which the diazo tests were positive. It has recently been suggested<sup>12</sup> that the substance producing the diazo reaction may be potassium indoxyl sulphate or possibly in part indoxyl glycuronate. Indican is one of the substances retained by the damaged kidney, and Krokiewicz<sup>25</sup> has recently pointed out the value of a knowledge of the indican content of the blood in nephritis. In the few cases of advanced nephritis to which we have applied this reaction definite indican retention was found, but the reaction did not seem to be as satisfactory as the diazo reaction.

The phenolsulphonphthalein test of Rowntree and Geraghty<sup>26</sup> is recognized as an accurate measure of renal function. In this work a positive diazo test was not obtained, except in one case in which the excretion of the dye exceeded 10 per cent. The phenolsulphonphthalein test is an accurate measure of the condition of the renal tissue, and since only positive diazo reactions have been obtained with extremely low phenolsulphonphthalein values, it can be assumed that this reaction (diazo) is obtained only in cases in which extensive renal damage has occurred. One can recall having seen numerous cases in which there was a comparatively high retention of nitrogenous products and excretion of a relatively normal amount of the dye. In some cases this condition no doubt has been due to some mechanical obstruction, while in others no apparent reason for the condition existed. In this type of case, a negative diazo reaction is usually found. Vascular disease in its late stages merges into renal disease, while the converse is also true, both terminate in the condition commonly known as uræmia. From the terminating symptom-complex one can hardly state the predominating lesion. But we believe that renal disease predominates in those cases presenting low phenolsulphonphthalein values and a positive diazo reaction. Owing to the remarkable variety and different combinations of symptoms that when taken together may be classed as uræmia, one can see that probably many conditions are labeled as uræmia that probably fall far short of definite renal disease. Consequently, in many supposed cases of uræmia a negative reaction is obtained. It has been our experience that the diazo reaction is confined definitely to those cases in which renal

25 Krokiewicz, A. *Virchows Arch f path Anat* **266** 239, 1927.

26 Rowntree, L. G., and Geraghty, J. T. *J Pharmacol & Exper Therap* **1** 231, 1910.



disease predominates. No case has been found in which there was a normal blood urea and creatinine and elimination of phenosulphonphthalein and a positive diazo reaction.

#### CONCLUSION

1 The diazo reaction is a simple test for advanced renal damage which can be performed with the most meager laboratory equipment.

2 A positive test was never found to accompany normal or low elimination of phenolsulphonphthalein.

3 A positive test was always found to be associated with a marked retention of nitrogenous products.

4 The test was found to be of considerable prognostic aid in the cases of advanced or extensive renal damage.

# PERFORATIONS OF THE COLON IN CHRONIC ULCERATIVE COLITIS \*

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The complications and sequelae of chronic ulcerative colitis place it in the category of serious diseases. Chronic ulcerative colitis means a definite disease entity presenting characteristic clinical, proctologic, roentgenologic and pathologic observations. Clinically, it is characterized by exacerbations and remissions, and occasionally by acute fulminating infection. During the active stage of the disease, foul-smelling mucus, pus and blood are discharged from the rectum, often associated with almost intractable diarrhea. The latter depends on the extent of involvement of the colon and the severity of the infections so that the patient may complain of constipation associated with frequent passages of blood and pus, particularly if the lesions involve only the rectum and the rectosigmoid.

Thus, because of few pathognomonic symptoms of chronic ulcerative colitis the disease may be confused with amebiasis, tuberculosis, a malignant condition, typhoid fever and other lesions of the colon. According to Buie,<sup>1</sup> however, the disease presents a typical proctoscopic picture, and Carman and Moore<sup>2</sup> have shown the roentgenologic aspects to be pathognomonic. Another important diagnostic criterion is the demonstration of the causative organism.<sup>3</sup> The injection of this organism into animals has produced lesions in the colons of rabbits and dogs in all essentials like those found in man.

The seriousness of chronic ulcerative colitis is due to complications and sequelae, such as polyposis,<sup>4</sup> a malignant condition,<sup>5</sup> stricture, hemorrhage, perinectal fistula and abscess, endocarditis, splenomegaly,

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\* Submitted for publication, Oct 30, 1928

<sup>1</sup> From the division of medicine, The Mayo Clinic

1 Buie, L A. Chronic Ulcerative Colitis, *J A M A* **87** 1271 (Oct 16) 1926

2 Carman, R D, and Moore, A B. The Roentgenologic Findings in Ulcerative Colitis, *Am J Roentgenol* **16** 17, 1926

3 Bargaen, J A. Chronic Ulcerative Colitis. Bacteriologic Studies and Specific Therapy, *Tr Am Proctol Soc* **28** 93, 1927

4 Logan, A H. Chronic Ulcerative Colitis. A Review of 117 Cases, *Northwest Med* **18** 1, 1919

5 Bargaen, J A. Chronic Ulcerative Colitis Associated with Malignancy, *Arch Surg* **17** 561 (Oct) 1928

mesenteric thrombosis, ocular phenomena, tetany, severe anemia, arthritis and perforation, the latter occurring when the ulcer extends deeply. It may lead to local or generalized peritonitis or to an abscess.

In The Mayo Clinic records from January, 1923, to July, 1928, twenty-two cases in which perforation occurred (3.4 per cent) were noted in 647 cases of chronic ulcerative colitis. In several other cases, the cause of death was believed to be perforation, but the complication occurred at the patients' homes, and the data, therefore, were incomplete, these cases are not included in this series. Sixteen of the twenty-two patients died, a mortality rate of 72.7 per cent. The diagnosis of perforation was made during life in eighteen cases, in six it was confirmed by operation, and in four of these by necropsy also. In the four other cases, the diagnosis was made at necropsy. Twelve of the twenty-two patients were operated on. Perforation had occurred before operation in five cases, operation was undertaken as an emergency measure in only two cases. In two of the cases, perforation occurred on the third and fifth days, respectively, after operation. In the remaining five cases, sufficient time had elapsed so that the operation could not be considered an exciting cause. Ileostomy was usually performed, although in two cases abscesses were drained. The age of the patients varied from 13 to 65 years, although fifteen of them were between the ages of 35 and 50.

The duration of the disease (from two months to thirty-five years) seemed to have little bearing on the incidence of perforation. The extent of involvement was more significant, in seventeen of the twenty-two cases, the entire large bowel was diseased.

The perforation was in the sigmoid portion of the colon in ten cases, in the cecum in three cases, in the rectum in two cases and in the splenic flexure in one case, in two cases there were multiple perforations of the colon. Two patients died of peritonitis, but necropsy failed to reveal a definite site of perforation. In two other cases, the home physician attributed death to perforation, but the site was not stated.

Three types of perforation may be noted: acute, chronic and multiple. Among the many symptoms, abdominal pain, cramps, tenderness and rigidity are most common. Pain was present in thirteen cases, tenderness in seventeen, rigidity in thirteen and cramps in all. The temperature was high in nine cases and subnormal in one case. The maximal leukocyte count was 20,000, leukocytosis being found in six cases, it was not recorded in some of the others. A mass was palpated in seven cases. Hemorrhage, or an increased amount of blood in the stools, occurred in six cases. Nausea, vomiting, thready pulse, chill, burning at the site of perforation, hiccup, delirium or shock may occur.

The treatment which was being given at the time of perforation did not seem to have a bearing on the condition. The treatment as a rule

is expectant ice bags or hot stupes to the abdomen, nothing by mouth, subcutaneous injections of sodium chloride solution, intravenous injections of a solution of dextrose and sodium chloride, opiates to keep the patient quiet and transfusion if the loss of blood indicates such a measure. Fibrinogen, a digitalis preparation, caffeine, etc., were given as stimulants in certain cases.

#### ILLUSTRATIVE CASES

CASE 1—A man, aged 35, registered at The Mayo Clinic in 1925, complaining of weakness and the intermittent discharge of blood and pus from the rectum for two years.

Results of a general examination were essentially negative except for a temperature of 100.4 F. The hemoglobin content was 71 per cent, the erythrocytes numbered 4,200,000 and the leukocytes 6,700. Three examinations of the stools did not reveal parasites or ova, but a great deal of pus and blood was found. The proctologist reported that the mucosa bled easily, that many irregular ulcers were seen and that the bowel was contracted one-fourth. The condition was diagnosed as chronic ulcerative colitis. The patient was admitted to the hospital, where the temperature ranged from 99 F to 103 F. Treatment with vaccine, bismuth subnitrate, camphorated tincture of opium, kaolin and tincture of iodine was instituted with a resultant slight decrease in the temperature. Three weeks after admittance to the clinic, sudden severe, cramping, abdominal pains developed, and the number of stools increased. The temperature was 101 F and the pulse rate 120. Tenderness and rigidity were elicited on palpation over the sigmoid. Hiccup then aggravated the condition. A diagnosis of subacute perforation was made, and intravenous injections of dextrose and sodium chloride solution were given. All treatment by mouth was stopped, and ice bags were placed on the abdomen.

The patient gradually grew weaker, vomited dark blood, passed about 4 liters of blood by rectum and died four days after the onset of the acute symptoms. Necropsy revealed ulcerative colitis with acute exacerbation and hemorrhage, recent perforation of the sigmoid with localized peritonitis and adhesions, terminal bronchopneumonia and hemorrhage into the stomach from dilated venules of the esophagus.

CASE 2—A boy, aged 15, entered The Mayo Clinic in 1926, because of diarrhea of four years' duration. He was having from five to six loose, watery stools a day, and occasionally tarry stools.

The patient was sallow and pale. The liver and spleen were palpable. The temperature was 99.2 F. The hemoglobin content was 45 per cent, the erythrocytes numbered 3,390,000 and the leukocytes 17,200. Results of examinations of the stools for parasites and ova were negative, but a great deal of pus and blood was found. The proctoscopic examination revealed multiple pinpoint scars and ulceration in the rectum and sigmoid, a few areas of larger ulceration scattered about in the rectum and ring contraction to 1 cm, 7 cm from the anal margin. A diagnosis of chronic ulcerative colitis and stricture of the rectum was made. The roentgenograms also showed chronic ulcerative colitis. The patient was given vaccine and began to improve slowly. During the course of treatment, he complained of acute tenderness in the left lower quadrant, which made it difficult to walk. Reexamination disclosed a nodular, sausage-shaped, tender mass which seemed to be attached to the colon. Perforation of the sigmoid and abscess was the diagnosis.

A permanent ileostomy of the modified Brown type was made. The abdomen contained free fluid. The cecum and ascending colon were thick and edematous. The mass in the left side was not explored. The patient's progress was satisfactory for one week, then the abdomen became distended and tense, and ascites developed. The temperature was 100.4 F and the pulse rate 140. Death occurred on the fifteenth day after operation. Necropsy revealed ileostomy for chronic ulcerative colitis and general peritonitis, splenomegaly and hypertrophic juvenile cirrhosis, marked thickening of the entire colon and partial obstruction at the sigmoid with a perisigmoidal inflammatory mass.

CASE 3—A woman, aged 37, entered The Mayo Clinic in December, 1927, complaining of bloody diarrhea of ten years' duration. Remissions and exacerbations were frequent, the latter being accompanied by a discharge of pus and blood.

The patient was underweight. The abdomen was tense and tender. The temperature was 101.5 F and the pulse rate 130. The hemoglobin content was 56 per cent, the erythrocytes numbered 3,540,000 and the leukocytes 9,900. The stools did not contain parasites or ova, but much blood and pus. The proctoscopic examination revealed that the mucous membrane was scarred in some areas, and that in other areas there were superficial, irregular ulcers of varying sizes. Slight spasm was noted in the lower half of the rectum where the mucosa appeared granular. A diagnosis of chronic ulcerative colitis was made, although the signs were not as marked as might have been suspected from the history. The roentgenograms showed chronic ulcerative colitis.

The patient was given immune chronic ulcerative colitis serum, the fever subsided, and the stools decreased in number. Two months later, a chill accompanied by a temperature of 104 F and a pulse rate of 130 developed suddenly, this was followed by severe cramps, nausea and an increased amount of blood in the stools. The abdomen was distended, tender and rigid. The hemoglobin content was 50 per cent, the erythrocytes numbered 2,750,000 and the leukocytes 13,900. A diagnosis of subacute perforation was made.

Food and liquids by mouth were stopped immediately, subcutaneous and intravenous injections of dextrose and sodium chloride were given, and hot stupes were applied to the abdomen. Six days later, the abdomen was moderately soft, and the cramps were less severe. The patient improved gradually. In three weeks, when she was dismissed, the temperature was normal, although she passed from six to ten stools daily. The subsequent course has been slow but progressive.

CASE 4—A man, aged 40, first entered The Mayo Clinic in 1925. He complained of intermittent discharges of blood and pus from the rectum for three years.

Results of the general examination were essentially negative. The hemoglobin content was 73 per cent, the erythrocytes numbered 4,320,000 and the leukocytes 7,000. Examination of the stools did not reveal parasites or ova, but much blood and pus. The proctoscopic examination disclosed edematous and granular mucosa with numerous small, irregular, easily bleeding ulcers throughout. The bowel was slightly contracted. Ulcerative proctosigmoiditis was diagnosed. Results of the roentgenologic examination of the colon were negative, owing to involvement of only the lower part of the sigmoid and rectum.

Autogenous vaccine was given, and the patient returned in six months, at which time he was having only one stool daily. The proctoscope showed the mucosa to be healed. Symptoms were then quiescent until January, 1928, when an exacerbation occurred. The general examination at this time revealed a tender, cordlike sigmoid. The proctoscopic examination showed that the mucosa was granular, and that it bled after slight trauma. The bowel was contracted about

one-third In spite of treatment, another exacerbation with fever and an increase in the number of stools containing blood and pus occurred two months later Diffuse abdominal pain, more localized to the left lower quadrant, was present, as were distention and tenderness The distention became acute, and the pain was localized to the right lower quadrant Acute appendicitis was considered, but owing to the severity of the colitis and the indefiniteness of the symptoms, operation was postponed The temperature ranged from 100 to 103 F, and the leukocytes from 8,000 to 15,000 The patient's condition remained about the same, and on the tenth day exploration was undertaken Gas escaped as soon as the peritoneum was opened Perforation of the sigmoid with diffuse peritonitis was found The patient died several days later

#### COMMENT

The serious nature of chronic ulcerative colitis cannot be overestimated Even with careful treatment by vaccine and serum, the patient's progress is often slow Although the results are much more promising than under the older regimen, many of the complications and the sequelae are still present The advent of any complication adds to the gravity of the prognosis Perforation is one of the most serious complications, although it frequently is not recognized The symptoms are usually definite, but they may be obscured by the extreme illness of the patient The treatment generally must be expectant, as operation offers little promise of cure The treatment for this grave condition is preventive, and this means the early recognition of chronic ulcerative colitis before it has progressed to involve the entire colon In order to recognize the disease early, the proctoscope must be used as a routine in all cases of diarrhea and bleeding from the rectum Earlier reports have shown that usually when the disease is recognized in the early stages, symptoms disappear under appropriate treatment

# THE METABOLISM IN PERNICIOUS ANEMIA \*

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BOSTON

The discovery of liver as a specific therapeutic agent in pernicious anemia<sup>1</sup> warrants the repetition of metabolic studies that have been performed with other modes of treatment

The protein and respiratory metabolism of five hospitalized patients with pernicious anemia was determined for periods varying from twenty to sixty-five days. These cases were under the direct supervision of Dr. Minot and Dr. Murphy, who were studying the effect of standardized liver extract and experimental liver fractions on the course of the disease. The nature of the effective fraction and the treatment of pernicious anemia with liver extract have been reported by the aforementioned observers in detail.<sup>2</sup> Since the response of the patient to a diet of whole liver was quite similar to his response to that of liver extract, it was thought that the metabolic changes with the two methods of administration would show a close resemblance

## EXPERIMENTAL PROCEDURE

Observations for cases 1 to 5 are recorded in tables 1 to 5, and are represented graphically for cases 1 to 3 in charts 1 to 3, respectively. Before treatment was begun, the erythrocyte counts in cases 1, 2, 3 and 4 were less than 2,000,000 per cubic millimeter, while in case 5, the count was 3,000,000. All the patients were women except the one in case 5, and none of them had received liver therapy in any form before entering the hospital. After a diagnosis was made, each patient was placed on a test liver fraction, if this proved to be ineffective after eight or ten days, a fraction of known potency was given. In cases 2, 3 and 4 fractions of little or no potency were received at first, thus allowing a control period of study before the effective fraction was given.

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\* Submitted for publication, Nov. 14, 1928.

\* From the Medical Clinic of the Peter Bent Brigham Hospital.

1 Minot, G. R., and Murphy, W. P. Treatment of Pernicious Anemia by a Special Diet, *J. A. M. A.* **87**: 470 (Aug. 14) 1926, A Diet Rich in Liver in the Treatment of Pernicious Anemia. Study of One Hundred and Five Cases, *ibid.* **89**: 759 (Sept. 3) 1927.

2 Cohn, E. J., Minot, G. R., Fulton, J. F., Ulrichs, H. F., Sargent, F. C., Weare, J. H., and Murphy, W. P. The Nature of the Material in Liver Effective in Pernicious Anemia, *J. Biol. Chem.* **74**: 69, 1927. Minot, G. R., Murphy, W. P., and Stetson, R. P. The Response of the Reticulocytes to Liver Therapy, Particularly in Pernicious Anemia, *Am. J. M. Sc.* **175**: 581, 1928.

TABLE 1—Protein and Respiratory Metabolism in Pernicious Anemia, Case 1

[illegible]



The response of the reticulocytes and the erythrocytes to effective liver fractions correspond to the responses reported by Minot and Murphy<sup>3</sup> There was a rapid increase in the percentage of reticulocytes in the blood, from about five to seven days after the liver therapy was begun, the elevation continued for about nine days thereafter. The

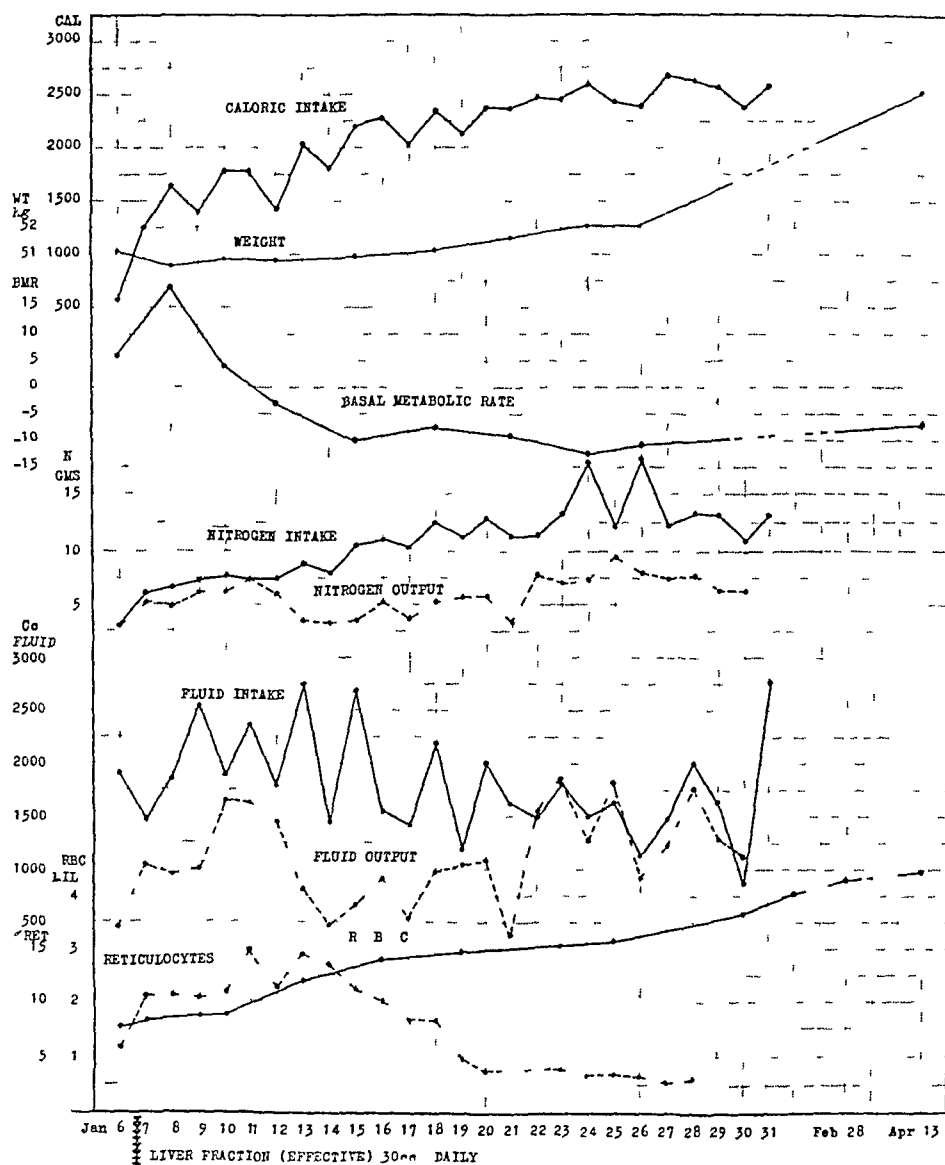


Chart 1—Graphic representation of observations in case 1

erythrocyte count showed a gradual and continuous increase beginning with the rise in the number of reticulocytes. All the patients left the hospital before the red blood cell counts reached normal. Several

3 Minot, G R, Cohn, E J, Murphy, W P, and Lawson, H A. Treatment of Pernicious Anemia with Liver Extract. Effects upon the Production of Immature and Mature Red Blood Cells, *Am J M Sc* **175** 599, 1928. Minot, Murphy and Stetson (footnote 2 second reference)

months later, however, the patients in cases 1, 2 and 5 were found to have about 4,500,000 cells per cubic millimeter

*Caloric Intake*—A diet rich in fruit and vegetables and low in fat, as described by Murphy and Minot,<sup>4</sup> was given to each patient when treatment was begun. Whole liver was omitted except in case 3, in which it was given several days before the patient was discharged from the hospital, because of a shortage of the extract. In cases 1, 2 and 5, the patient received no meat at any time. The daily caloric intake was voluntary on the part of the patient, who was seen each day by a dietitian in order that whims as to quality and quantity of food could be cared for as well as possible. Refused food was weighed and the daily caloric intake was computed. Either a decreased appetite or marked anorexia was noted during the control period, that is, while ineffective treatment was being given. A few days after beginning the standardized extract, usually just before the increase in the number of reticulocytes began, there was a striking improvement in the general feeling of the patient, and a marked increase in appetite. In case 1, the patient could not eat enough at mealtime to prevent a craving for food that came on between meals and at night, whereas before treatment she had no desire for food, in case 2, the patient had an increased intake of 1,000 calories per twenty-four hours within two days, while in case 3 a similar increase was noted within ten days. This rapid improvement of appetite and general feeling is an indication that a remission has begun and often occurs before there are any demonstrable changes in the peripheral blood. It is of aid clinically in evaluating the progress of cases in which numerous examinations of the blood may be impracticable.

#### NITROGEN METABOLISM

The literature on nitrogen metabolism indicates that the nitrogen balance in pernicious anemia is frequently negative (that is, the output exceeds the intake), especially during the more severe stages of the disease.<sup>5</sup> Rosenquist,<sup>6</sup> in a study of several cases, found that the nitrogen balance varied from day to day between positive and negative values. Minot<sup>7</sup> and Pepper and Austin<sup>8</sup> each determined the nitrogen

4 Murphy, W. P., and Minot, G. R. A Special Diet for Patients with Pernicious Anemia, Boston M. & S. J. **195** 410, 1926

5 Pearce, R. M., Krumbhaar, E. B., and Frazier, C. H. The Spleen and Anemia, Philadelphia, J. B. Lippincott Company, 1918, p. 231

6 Rosenquist, E. Ueber den Eiweissstoffwechsel bei der perniciosen Anämie, mit specieller Berücksichtigung der Bothriocephalus-Anämie, Ztschr. f. klin. Med. **49** 193, 1903

7 Minot, G. R. Nitrogen Metabolism Before and After Splenectomy in a Case of Pernicious Anemia, Bull. Johns Hopkins Hosp. **25** 338, 1914

8 Pepper, O. H. P., and Austin, H. J. Metabolism Studies Before and After Splenectomy in a Case of Pernicious Anemia, Arch. Int. Med. **18** 131 (July) 1916

TABLE 2—*Protein and Respiratory Metabolism in Pernicious Anemia, Case 2*

Date, 1927	Red Blood Cells per Cubic Millimeter	Reticu- locytes, per Cent	Protein Intake, Gm	Caloric Intake	Fluid Intake, Cc	Urine Output, Cc	Nitrogen, Gm		Weight, Kg	Basal Metabolism			Liver Fraction
							Intake (plus Fraction for Feces)	Urine		Total Calories per Hour	B M R per Cent (DuBois)		
Nov 25	1,160,000	5.5	56	1,288	1,660		10.0		51.0	51.8	— 6		40 cc (noneffective)
26		5.7	31	1,104	980	718	6.0	7.0	53.4	50.7	— 7		40 cc fraction)
27			37	1,322	1,110	540	7.0	5.3					40 cc
28	1,830,000	3.2	23	1,019	1,420	525	4.7	5.3					40 cc
29	1,780,000	2.3	33	1,136	820	375	6.3						40 cc
30		1.7	27	944	1,590	630	5.3	8.7	53.3	16.1	— 16		10 cc
Dec 1	1,780,000	1.4	35	1,387	1,230	110	6.6	3.7					40 cc (effective)
2		1.8	21	904	1,800	395	1.4	1.4					100 cc fraction)
3	1,800,000	1.3	19	985	3,800	525	1.0	3.4					100 cc
4			18	723	2,950	510	3.9	1.0					100 cc
5	1,810,000	2.1	20	1,041	2,510	510	5.6						100 cc
6		4.0	18	1,881	1,700	325	8.7		52.8	52.3	— 4		100 cc
7	1,810,000	9.6	59	1,979	1,900	655	10.4	1.7					100 cc
8	2,180,000	11.2	51	1,755	1,400	525	9.0	7.7					100 cc
9		10.2	31	1,469	1,310	353	6.4	2.6					100 cc
10	2,540,000	8.2	48	1,943	1,750	820	8.7	5.2					100 cc
11		6.8	38	1,752	1,700	565	7.1	5.9	72.9	39.3	— 28		100 cc
12	2,340,000	2.4	15	1,764	1,150	1,075	8.2	8.4					4 vials (more effective)
13	2,920,000	2.3	14	1,759	1,350	610	8.0	1.4					4 vials fraction)*
14	2,710,000	3.9	38	1,515	2,000	590	7.1	5.0					4 vials
15	3,000,000	3.8	50	1,977	1,850	925	9.0	1.8					4 vials
16	3,250,000	6.4	61	2,169	1,530	845	10.8	3.6					4 vials
17	3,160,000	3.5	45	1,823	2,325	950	8.2	4.0	52.8	49.3	— 9		4 vials
18			40	1,665	1,650		8.4						4 vials
19													
20													
1928													
Jan 3	4,470,000								53.8	47.1	— 14		
April 13	4,500,000								57.9	68.3	+ 20		

\* Each vial contained approximately 5 Gm powdered liver extract

metabolism in a case of pernicious anemia before and after splenectomy. Before operation, the former found a negative balance and the latter a slightly positive balance, while after operation, both cases showed a definite retention of nitrogen or positive balances. Gibson and Howard<sup>9</sup> reported more positive than negative balances in their

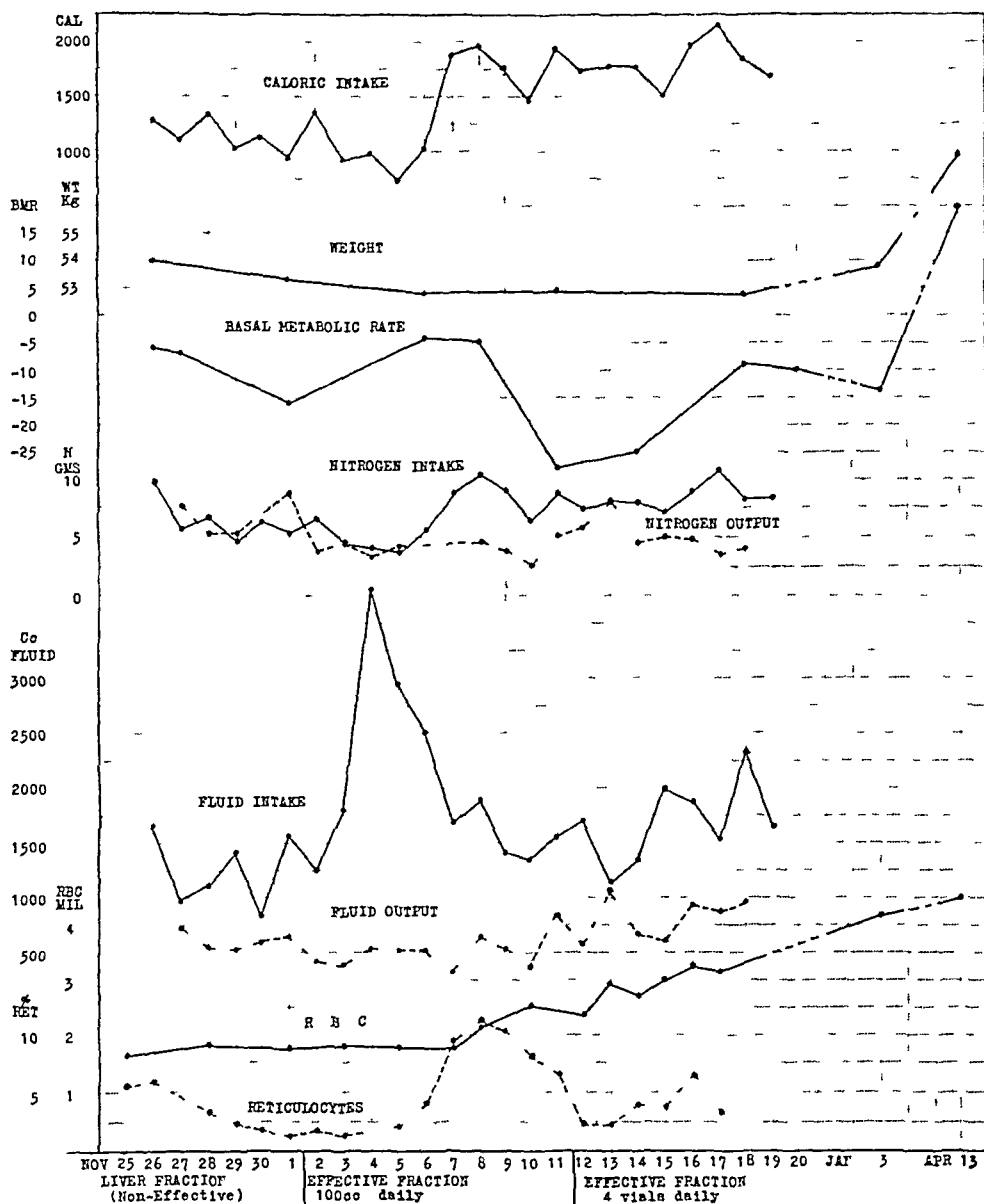


Chart 2—Graphic representation of observations in case 2

series. Becker,<sup>10</sup> in a study of eight patients, found periods in four of them when the balance was negative, in each instance, this fact could be attributed to a decreased intake of protein, fever or the severity of the

9 Gibson, R. B., and Howard, C. P. Metabolic Studies in Pernicious Anemia, *Arch Int Med* **32** 1 (July) 1923

10 Becker, G. Studien über den Stoffwechsel bei perniziöser Anämie, *Acta med Scandinav* **63** 478, 1925-1926

TABLE 3—*Protein and Respiratory Metabolism in Pernicious Anemia, Case 3*

Date, 1928	Red Blood Cells per Cubic Millimeter	Reticu- locytes, per Cent	Protein Intake, Gm	Calorie Intake	Fluid Intake, Cc	Urine Output, Cc	Nitrogen, Gm			Weight, Kg	Basal Metabolism			Liver Fraction
							Intake (plus Faction)	Urine (plus 1 Gm for Feces)	Balance		Total Calories per Hour	B	M	R
March 13	1,150,000	19	11	548	875		26			50.8				3 vials (partially effective)
14		22	20	1,135		605	40	67	-22					3 vials effective
15		23	20	969	1,900		45	104	-51					3 vials
16		15	23	1,036	1,760	1,040	53	104	-15		58.1	+13		3 vials
17		23	28	1,036	1,760	620	53	60	-15					3 vials
18		23	23	912	1,100	610	10	62	-22					3 vials
19		32	20	955	1,200	1,220	0	132	-132		55.7	+9		3 vials
20	1,050,000	69	0	240	900		19	144	-125					3 vials
21	1,225,000	74	7	355	850	1,550	19	83	-34					3 vials
22		11.5	26	977	1,130	655	49	83	-34					3 vials
23		10.2	17	813	930	600	35	70	-35		50.2	+16		3 vials
24			24	1,132	1,100	790	16	85	-39					3 vials
25			26	856	1,000	685	19	96	-17		55.8	+9		6 vials no 343†
26		11.1	26	1,317	1,160	335	65	45	+20					6 vials (effective fraction)
27	1,200,000	12.2	31	1,185	1,185	575	68	65	+0.8					6 vials
28		14.5	33	1,235	1,320	400	56	48	+0.8	17.6	47.7	-5		6 vials
29		15.7	25	1,222	1,320	280	70	35	+3.5					6 vials
30		13.7	34	1,102	1,030		65	49	+1.6					6 vials
31	1,300,000	14.4	31	1,631	1,360	330	70	58	+1.2		15.6	-3		6 vials
1 April		19.0	34	1,770	1,310	975	93	57	+3.6					6 vials
2		12.8	48	1,670	1,000	975	86	50	+10.1		48.1	-3		6 vials
3	1,600,000	16.2	44	2,080	2,940	950	149	15	+4.1					6 vials
4	2,050,000	10.1	52	2,024	1,410	750	120	64	+6.5					6 vials
5		8.7	53	2,022	1,860	1,275	100	59	+7.9		50.1	-0		6 vials
6			71	2,060	990	1,310	120	19	+5.1	48.1	47.8	-1		6 vials
7			70	1,967	1,710	820	128	70	+5.2					6 vials
8	1,330,000	3.1	66	2,321	1,500	1,353	122	55	+7.5					6 vials
9			56	1,751	1,200	1,175	106	61	+0.9					6 vials
10			75	2,224	1,450	1,275	136	51	+6.8					6 vials
11	2,055,000	1.7	16	553	795	600	12	62	+6.8					6 vials
12			71	2,419	1,240	930	130	70	+8.6					6 vials
13			66	2,117	1,140	670	122	15	+9.7		61.6	+23		3 vials no 343
14			64	2,188	1,490	845	118	53	+9.1					3 vials
15	2,200,000		79	2,414	1,100	990	142	51	+7.6	47.9	52.9	+6		3 vials
16			69	2,167	1,330	1,000	126	50	+7.2					3 vials
17			65	2,262	1,300	700	120	48	+10.2					3 vials
18	3,230,000		69	2,404	1,400		126	18	+8.6	48.8	60.0	+19		3 vials
19			84	2,749	1,330	730	150	70	+9.7					3 vials
20			86	2,458	1,300	1,235	136	56	+9.4					3 vials
21			79	2,615	1,580	730	112	15	+7.7					3 vials
22	3,200,000		92	2,714	1,480	425	154	17	+10.3					3 vials
23			82	2,480	1,500	800	148	54	+11.4					3 vials
24			97	2,728	1,100	740	167	53	+13.6					3 vials
25	3,140,000		103	2,656	1,370	730	150	61	+13.6					3 vials
26			82	2,437	1,300	780	138	58	+12.6					3 vials
27			115	2,788	1,290	580	184	49	+10.3	19.2	52.0	+1		3 vials
28			93	2,564	1,630	450	152	60	+13.6					3 vials
29			92	2,786	1,200	910	117	65	+13.6					3 vials
30			120	2,821	1,350	720	102	68	+10.3					3 vials
1 May			107	2,975	1,200	935	171	75	+12.2	19.9	59.6	+17		3 vials
2	3,300,000		123	2,685	1,300	910	107	75	+12.2					3 vials
3			123	3,111	1,410		107	75	+12.2					3 vials
4			96	2,583	1,550		154		+15		58.7	+15		3 vials
5	3,700,000													3 vials

\* Each vial contained approximately 5 Gm powdered liver extract

† No 343 denotes the standardized powdered extract furnished by Eli Lilly &amp; Co

disease. Otherwise, he obtained positive balances which not infrequently reached values of from 4 to 8 Gm of nitrogen per twenty-four hours. Weiksel<sup>11</sup> stated that there is always a negative nitrogen balance during a relapse and possibly a positive balance during a remission. Shortly after transfusions of blood, he found increased negative balances which he explained on the theory that the residual blood was washed out at this time and that some tissue protein was carried along with it. Mosenthal<sup>12</sup> reported improvement in three cases of pernicious anemia on forced feedings. One of his patients

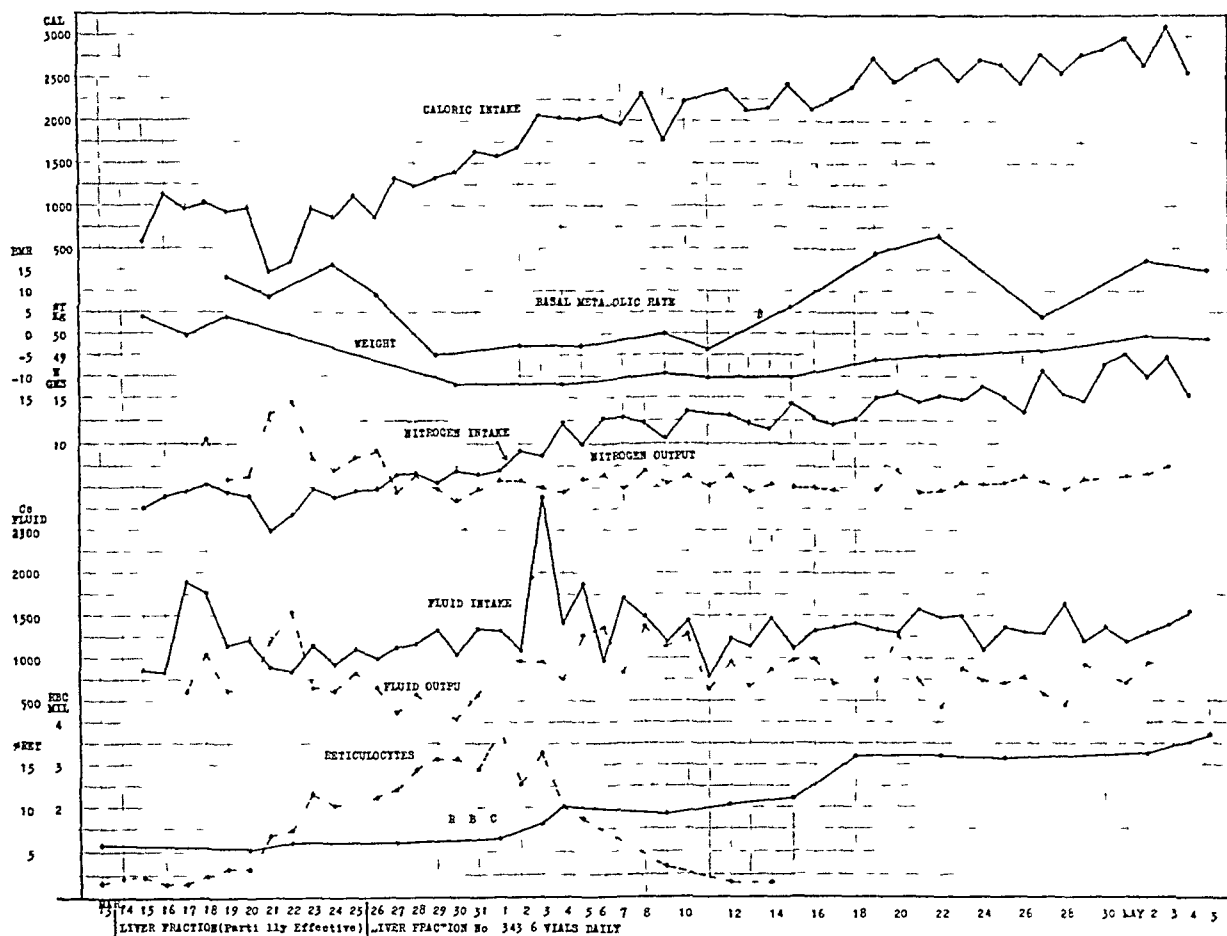


Chart 3—Graphic representation of observations in case 3

had an increase in the red blood count from 1,000,000 to 3,700,000 cells per cubic millimeter within a month, at the same time, the nitrogen balance changed from negative to markedly positive values. The nitrogen balance is largely dependent on the circumstances of the individual case of pernicious anemia, for this reason, the results in the literature are not consistent.

11 Weiksel, J. Ueber den Eiweissstoffwechsel bei perniziöser Anämie nach Bluttransfusionen, *Ztschr f klin Med* **105** 332, 1927.

12 Mosenthal, H. O. The Effect of Forced Feeding on the Nitrogen Equilibrium in a Case of Pernicious Anemia, *Bull Johns Hopkins Hosp* **29** 129, 1918.

*Results*—In this series, before the treatment became effective, cases 2, 3 and 5 showed definitely negative nitrogen balances. In cases 1 and 4, a negative balance was observed on the first day of study only, therapy was then started, and no control period was obtained.

The twenty-four hour urinary nitrogen was determined by the micro-Kjeldahl method. Nitrogen in the feces was not determined in a routine manner, 1 Gm being added to the daily urinary nitrogen to obtain the approximate total nitrogen excretion per day. The nitrogen intake was computed both from the protein in the food and from the nitrogen in the liver extracts which contained no protein. In the course of the remission, it was found to increase with the general caloric intake. The output of nitrogen decreased definitely about the time of the rise in the number of reticulocytes, then it increased slightly and maintained a more or less constant low level throughout the period of observation. In other words, positive nitrogen balances occurred shortly after an effective fraction was begun. As the patient's condition improved, they became increasingly more positive. During the periods of the most marked retention of nitrogen (from 8 to 10 Gm per twenty-four hours in cases 3 and 4), determinations of fecal nitrogen for twenty-four hours showed figures of less than 1 Gm on several occasions, which makes the possibility of a large amount of loss in the feces during this stage unlikely. No cases were studied throughout the entire period of erythrocytic regeneration, but it is supposed that the nitrogen balance would assume normal proportions as the blood level approached 5,000,000 red blood cells per cubic millimeter.

This markedly increased deposit of protein observed may be utilized by the bone marrow in its increased regenerative function, but more likely it is chiefly used to supply the protein-starved tissues throughout the body.

*Water Balance*—During the rise in the number of reticulocytes, the output of urine in the twenty-four hours diminished, then it increased gradually and later during remission equaled, and at times exceeded, the intake of fluid. In cases 1 and 4, there was a gradual decrease in the intake of fluid throughout the period studied. An unusually high intake was observed in case 2 following the administration of an effective fraction. This high intake along with the diminished output seen in all the cases may be explained by an increased demand for water at the most active stage of the regeneration of red cells. The later increase in output may be the result of (1) greater fluid content of the large diet or, (2) possibly, a loss of fluid from the tissues, since edema is a common observation in pernicious anemia.

TABLE 4—*Protein and Respiratory Metabolism in Pernicious Anemia, Case 4*

Date, 1928	Red Blood Cells per Cubic Millimeter	Reticu- locytes per Cent	Protein Intake, Gm	Chloric Intake	Fluid Intake, Cc	Urine Output, Cc	Nitrogen Gm		Weight Kg	Basal Metabolism		Liver Fraction
							Intake (plus Fraction) for Feeces	Urine		Total Calories per Hour	B M R per Cent (DuBois)	
March 16	1,420,000	3.3	26	1,084	800	1,225	4.2		70.3	66.0	+ 9	60 cc (slightly effective friction)
17		2.1	48	1,806	2,650		7.7	11.2				60 cc
18		2.4	48	1,806	2,650	540	7.0	5.1	70.8	65.9	+ 8	60 cc
19		2.6	44	1,565	1,760	800	7.8	5.8				60 cc
20	1,520,000	3.7	49	1,688	2,400	760	11.3	6.0	70.6	61.8	+ 2	60 cc
21		3.6	71	1,934	1,140		12.4	4.5				60 cc
22	1,350,000	5.5	78	2,111	1,240	650	12.4	4.5	71.0	61.3	+ 2	60 cc
23		4.8	46	1,382	1,900	1,240	7.3	6.8				60 cc
24	1,530,000	5.3	76	1,891	1,700	1,315	12.1	7.9	71.2	57.5	— 5	80 cc (effective friction)
25			67	2,044	2,450	630	10.7	6.4				80 cc
26	1,560,000	4.3	68	2,189	1,010	625	11.8	4.2	71.2	60.1	— 1	80 cc
27		5.3	73	1,758	2,000	525	12.5	3.0				80 cc
28	1,660,000	5.4	63	1,836	1,700	1,230	11.0	6.7	71.2			80 cc
29		5.7	52	1,797	2,025	540	9.0	3.7				80 cc
30		14.5	64	2,084	1,990	240	11.2	2.4				80 cc
31	1,630,000	10.2	65	1,797	1,800	1,370	11.4	5.5	71.0	61.7	+ 2	80 cc
April 1		10.4	67	2,189	950	600	11.7	3.7				80 cc
2		12.7	67	1,926	1,300		11.7					80 cc
3	2,210,000	14.8	68	2,114	1,000	630	11.8	4.1	70.8	54.8	— 9	80 cc
4		10.3	85	2,317	1,270	355	11.8	3.5				80 cc
5	2,210,000	8.2	68	2,301	1,500	955	14.4	5.0	71.2	50.1	— 17	80 cc
6		7.0	84	2,440	1,600		15.0	9.7				80 cc
7			88	1,670	1,400	2,000	12.0	4.5	71.2	45.7	— 20	80 cc
8			69	1,933	1,800	710	17.0	5.9				80 cc
9	2,540,000	6.1	106	2,117	1,800	910	14.6	5.5				80 cc
10			85	2,153	1,650	820	14.6	5.5				80 cc
11	2,550,000	5.5	72	1,970	2,000	1,235	12.5	5.9				80 cc
12			75	2,131	1,750	1,150	13.0	5.2	70.8	51.2	— 10	80 cc
13			95	2,357	1,250	1,640	16.2	5.5				80 cc
14	3,450,000	5.0	84	1,914	1,550	1,320	14.6	6.0				80 cc
15			77	2,144	1,300		13.3					80 cc
16	3,300,000	6.2	88	2,502	2,425	1,800	15.0	7.3				80 cc

\* No 113 denotes the standardized powdered extract furnished by Eli Lilly & Co



*Body Weight*—Changes in body weight during the period of hospitalization were negligible in all cases except case 3 in which 3 Kg were lost before a totally effective fraction was given. In cases 1 and 2 the patients had gained 5 Kg each when seen several months after leaving the hospital.

#### RESPIRATORY METABOLISM

The literature on the respiratory metabolism in pernicious anemia is reviewed by Meyer and DuBois,<sup>13</sup> Tompkins, Brittingham and Drinker,<sup>14</sup> Grafe<sup>15</sup> and Becker.<sup>10</sup>

Meyer and DuBois<sup>13</sup> found normal or only slightly elevated basal metabolic rates in mild cases and higher rates in severe ones. In five cases studied, the rates varied from plus 2 to 33 per cent of normal, and the respiratory quotients were within normal limits. Boothby and Sandiford,<sup>16</sup> in a report on the metabolic rate in conditions not due to disorders of the thyroid gland, included fifty-five cases of pernicious anemia and splenic anemia classified together, 10.6 per cent of which had rates over plus 20 per cent while the remaining cases fell between minus 15 and plus 15 per cent.

Tompkins, Brittingham and Drinker studied the effect of blood transfusions on the basal metabolism in pernicious anemia. In eleven cases the rates varied from minus 15 to plus 20 per cent of the normal rate, before transfusion the more recent acute cases having the higher, and the long-standing chronic cases the lower, values. Following transfusion in five cases of primary anemia, there was a drop in the pulse, respiratory activity and temperature and a response of the blood picture which occurred at once or within twelve hours, whereas the basal metabolism fell to the lower limit of normal or below only after a few days had elapsed. These authors cited the usual explanations for the increased metabolic rates noted in pernicious anemia, namely, (1) the increased muscular work caused by compensatory, respiratory and circulatory activity and (2) the increased need of the young red cells for oxygen. They then concluded that since the reduction of the metabolism lagged behind other factors following transfusion, the decrease was not

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13 Meyer, A. L., and DuBois, E. F. The Basal Metabolism in Pernicious Anemia, *Arch. Int. Med.* **17** 965 (June) 1916.

14 Tompkins, E. H., Brittingham, H. H., and Drinker, C. K. The Basal Metabolism in Anemia with Especial Reference to the Effect of Blood Transfusion on the Metabolism in Pernicious Anemia, *Arch. Int. Med.* **23** 441 (April) 1919.

15 Grafe, E. Die pathologische Physiologie des Gesamtstoff und Kraftwechsel bei der Ernährung des Menschen, *Ergebn. d. Physiol.* **21** 1, 1923.

16 Boothby, W. M., and Sandiford, I. Summary of the Basal Metabolism Data on 8,614 Subjects with Especial Reference to the Normal Standards for the Estimation of the Basal Metabolic Rate, *J. Biol. Chem.* **54** 783, 1922.

simply due to cessation of compensatory muscular activity. They suggested that the metabolism was dependent, for the most part, on two opposing factors outside of muscular activity: (1) some type of stimulation to the body cells, perhaps only to the blood-forming cells and (2) alterations in the tissues of the body, the former causing an increase and the latter a decrease in metabolism.

Becker,<sup>10</sup> in sixteen observations on the metabolic rate in seven patients with pernicious anemia, found variations from plus 1 to plus 28 per cent of the normal rate. One case showed a drop from plus 22 to plus 5 per cent within one and a half months, while the red cells increased from 2.3 to 4.3 million per cubic millimeter, a second case showed a fall from plus 20 to plus 11 per cent within a month, while the red count increased from 1.7 to 3.6 million. Neither of these patients received blood transfusions or a diet containing liver. Richards and Strauss<sup>17</sup> made three determinations of the basal metabolic rate on a patient with pernicious anemia while he was receiving liver therapy, the initial rate was plus 20 per cent, and a month and half later when the red count had risen, it had fallen to the level of the normal average.

The foregoing reports indicate that an increased metabolic rate is common in pernicious anemia, and that as the blood picture improves there is a tendency for the consumption of oxygen to fall from its previous level.

*Results*—In the five cases in this series, the metabolism was determined by the oxygen consumption method with Benedict-Roth portable machines. Before treatment, all the patients had metabolic rates between minus 12 and plus 13 per cent of the normal rate, according to DuBois' standards. Consistent changes occurred in the consumption of oxygen in every case during the remission which took place on liver therapy. An initial diminution of the rate was noted in those patients in whom a control period was made possible by ineffective fractions, this is in keeping with the rapid decline in the general condition of patients with pernicious anemia that is often seen when they receive complete rest in bed without other treatment. In cases 2, 3 and 4, the patients became definitely worse in the few days before a potent fraction was given, and the fall in the metabolic rate may be attributed to progressive malnutrition and asthenia. The next change in the rate was observed at the beginning of the rise in the number of reticulocytes, when it showed an average increase of 10 points in per cent. At this stage, there is a sudden outpouring of young red cells into the blood stream and a relief of congestion in the bone marrow, which

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<sup>17</sup> Richards, D. W., and Strauss, M. L. Circulatory Adjustment in Anemia, *J. Clin. Investigation* **5** 161, 1928.

TABLE 5—*Protein and Respiratory Metabolism in Pernicious Anemia, Case 5*

Date, 1927		Red Blood Cells per Cubic Millimeter	Reticu- locytes, per Cent	Protein Intake, Gm	Caloric Intake	Fluid Intake, Cc	Urine Output, Cc	Nitrogen, Gm			Weight, kg	Basal Metabolism		Liver Fraction
								Intake (plus 1 Gm Fraction) for Feces)	Urine	Balance		Total Calories per Hour	B M R per Cent (DuBois)	
Dec	1	3,100,000	0.7								61.5	58.8	-12	60 cc (effective fraction)
	2		0.6				770	10.1	10.5	-0.4				60 cc
	3	3,050,000	0.6	57	2,048	910	805	11.6	12.8	-1.2				60 cc
	4		0.6	66	2,230	860		9.3	10.3	-1.0				60 cc
	5	3,300,000	0.6	52	1,659	925	780	12.4	14.0	+8.4				60 cc
	6		0.4	71	2,458	1,010	484	12.0	14.3	-2.3				60 cc
	7	2,865,000	1.0	69	2,402	860	940	13.6	7.3	+6.3				60 cc
	8		1.6	79	2,744	920	635	11.7	8.6	+3.1				60 cc
	9	3,500,000	2.2	67	2,438	910	840	12.8	11.9	+0.9	62.9	60.4	-9	60 cc
	10		2.4	80	2,729	1,020	1,215	12.3	7.5	+4.8				60 cc
	11		1.7	77	2,808	800	650	14.3	8.2	+6.1				60 cc
	12	3,240,000	1.1	83	2,920	960	725	14.3	8.8	+5.5				60 cc
	13		1.1	83	2,669	720	1,100	14.8	9.7	+5.1				60 cc
	14	3,190,000	1.4	86	2,700	1,010	1,225	14.6	10.0	+4.6				60 cc
	15	3,450,000	1.2	85	2,808	870	970	15.0	8.4	+6.6				60 cc
	16	3,450,000	1.0	88	2,728	710					63.4	55.5	-17	60 cc
	17		1.1											60 cc
1928														
Jan	3	4,530,000									64.1	64.6	-4	

probably results in an overactivity of the blood-forming tissues, this would account for the transient rise in basal metabolism. It is interesting to note that in case 2 the patient, who had a secondary rise in the number of reticulocytes following the administration of a more potent liver fraction beginning with December 12, had also a secondary rise in the consumption of oxygen. Following the increased metabolic rate during the rise in reticulocytes, there was a rapid fall averaging about 25 points in per cent in from eight to ten days. It remained at this low level during the more active stage of readjustment. This diminution in basal metabolism regardless of its previous level, is one of the most striking phenomena in the remission.

The changes can explain why Tompkins, Buttingham and Dinker<sup>14</sup> observed a delay of several days in the fall of the basal metabolism following blood transfusion, while the pulse, respiration and blood picture reacted almost immediately. A response in reticulocytes probably occurred in their series, and at this time the metabolic rate would not fall. Too few tests were made to note a rise at this time.

Many explanations have been given for the decrease in the metabolic rate observed during the improvement of patients with pernicious anemia but it seems that three of the marked general changes in physiology that occur at this time would be the most important influencing factors. First, active alterations in tissue are occurring, as is evidenced by the storage of protein and the loss of water. When ingested protein is deposited as new tissue its amino-acids exert no stimulating effect, or specific dynamic action on the metabolism<sup>18</sup> and loss of this effect may be seen in determinations of the basal metabolic rate made from day to day. Second, there is a rapid change of the type of cell predominating in the bone marrow. Peabody<sup>19</sup> has shown that a highly developed megaloblastic hyperplasia almost disappears during a remission while the normoblasts and normal red cells increase in number. The difference in the oxygen required by the embryonic type of cell and by the mature cells may manifest itself at this time. Third, there were average decreases of one degree in temperature, ten points in the minute pulse rate, and (in patients 2, 4 and 5) five points in the respiratory rate, all occurring within a few weeks after effective therapy was begun. Are these changes causal factors or merely the effect of a decreasing metabolism? The rôle of fever in elevating the metabolism is well known. The increases in pulse and respiratory activity in patients with severe anemia are considered compensatory factors in maintaining a normal metabolism, and their increased action per se would tend to

18 Lusk, G. The Science of Nutrition, Philadelphia, W. B. Saunders Company, 1923, p. 245.

19 Peabody, F. W. The Pathology of the Bone Marrow in Pernicious Anemia, *Am J Path* 3 179, 1927.

affect the consumption of oxygen. To sum up, tissue alterations, bone marrow changes and a reduction in pulse rate, temperature and respiratory rate would all seem directly related to a decrease in the metabolic rate, but the relative influence of each factor remains a question.

The general decrease in metabolic rate was not sustained at the low level first reached, but gradually increased as the blood picture approached normal, which indicates that the first low level did not represent the person's normal metabolism but rather the rate during a period of readjustment in the course of a remission.

#### COMMENT

The rapid metabolic changes in pernicious anemia occurring at the beginning of a remission on liver therapy confirm the high specificity of liver for this disease. The patient as first seen, with anorexia and weakness, is in marked contrast to the greatly improved patient seen after a week of treatment. A theory now held by many authors is that pernicious anemia is due to improper digestion in the stomach resulting in the lack of a substance necessary for normal cellular metabolism in the hemopoietic system. When the deficient substance is given in the form of liver, the red blood cells are able to mature properly, resulting in rapid changes in the blood picture and in the general metabolism. At this time, there is a striking retention of protein in the body, which is evidenced by the markedly positive nitrogen balances. The negative balances often observed in untreated patients with anemia probably lead to a general protein starvation, which is quickly relieved when the bone marrow is made to function properly. Or, besides relieving a general deficiency in protein, the protein deposited may be utilized appreciably by the blood-forming tissues in their active regenerative processes.

Speculation as to the cause of these metabolic changes during a remission may throw some light on the pathologic physiology of pernicious anemia.

#### SUMMARY

1 Metabolic studies were conducted in five cases of pernicious anemia during the early part of the remissions caused by liver extract.

2 The voluntary caloric intake increased rapidly a few days after treatment was instituted. This, with general subjective improvement, was often the first indication that a remission had begun.

3 A negative nitrogen balance, present at first in every case, became markedly positive while the patient was under treatment.

4 The output of urine decreased during the rise in reticulocytes and then increased, often exceeding the intake of fluid.

5 The body weight showed negligible variations early, and moderate increases later, in the remission

6 The basal metabolic rate, which was within normal limits before treatment, increased during the rise in the number of reticulocytes, fell rapidly and remained low during erythrocytic regeneration, and finally rose as the patient approached a normal state

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# ALKALOSIS OCCURRING IN ANEMIA (PROBABLY PERNICIOUS)

REPORT AND COMMENT ON A CASE<sup>\*</sup>

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In 1921, Van Slyke<sup>1</sup> classified nine theoretically possible variations in the acid base balance of the blood. The bicarbonate content of the blood may be high, low or normal, and in each of these conditions the  $p_H$  may be high, low or normal. All of these possibilities have been produced experimentally, and most of them have been found to occur clinically. These possibilities are illustrated in the chart by Van Slyke (fig 1). It is in the first class that the case here described falls, that of uncompensated alkali excess.

In recent years, many cases of alkalosis have been reported in the literature, and to explain this condition various causes have been ascribed,<sup>2</sup> as follows: (1) The administration of sodium bicarbonate, (2) pyloric or high intestinal obstruction, (3) fever, (4) deep roentgen therapy, (5) certain conditions of the gallbladder, (6) hyperpnea, (7) vomiting, (8) parathyroid deficiency and (9) nephritis associated with uremia.

It is of the last group that we will speak in particular. In 1925, Harrison and Perlzweig<sup>3</sup> reported a case of alkalosis not due to the administration of alkali but associated with uremia, which was strikingly similar to the case here discussed. A brief summary of their case is as follows: The patient was anemic, she had vomited considerably, there was no free acid in the gastric juice, the urine was always acid to litmus and, the chloride content of the blood was low (0.486), the nonprotein nitrogen, 250, the  $p_H$ , 7.6 (colorimetric method) and

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<sup>\*</sup> Submitted for publication, Sept 17, 1928.

From the service of Dr. L. F. Frissell, St. Luke's Hospital.

1 Van Slyke, D. D. *J. Biol. Chem.* **48**: 153, 1921.

2 Kast, L., Myers, V. C., and Schmitz, H. W. *Clinical Conditions of Alkalosis*, *J. A. M. A.* **82**: 1858 (June 7) 1924. Koehler, A. E. *Acid-Base Equilibrium*, *Arch. Int. Med.* **31**: 590 (April) 1923. Harrison, T. R., and Perlzweig, W. A. *Alkalosis, Not Due to the Administration of Alkali, Associated with Uremia*, *J. A. M. A.* **84**: 671 (Feb. 28) 1925. Foster, N. B. *The Parathyroid Glands*, *Nelson's System of Medicine*, New York, Thomas Nelson & Sons, 1926, p. 311.

3 Harrison and Perlzweig (footnote 2, third reference).

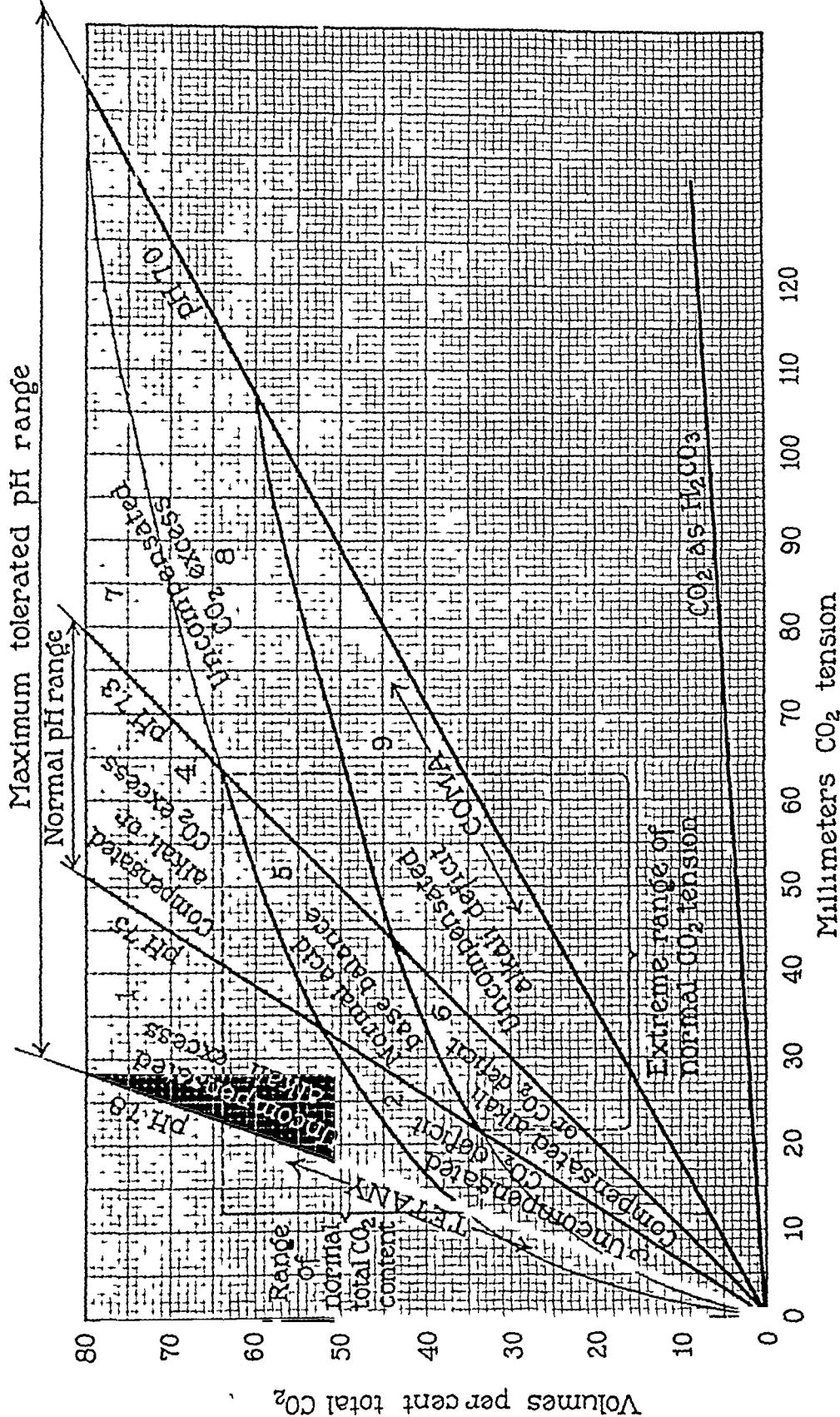


Fig 1—The relation of the bicarbonate in the blood to the  $p_{\text{H}}$



the carbon dioxide combining power, 65 per cent Autopsy revealed that one kidney was hydronephrotic and atrophied, and the other showed an advanced chronic nephritis

#### REPORT OF CASE

*History*—N B, aged 38, married, an Armenian, a tailor, was admitted to the medical service of St Luke's Hospital on July 12, 1926, complaining of weakness This condition, with dyspnea on exertion, had been progressive for four weeks During this time he noticed that his skin was assuming a pale orange hue He was forced to abandon his occupation two weeks before admission because of weakness He fainted twice during that time, once on the day of admission Following later attacks of syncope he had noticed palpitation

*Examination*—Physical examination disclosed the patient to be well nourished, with skin of a lemon yellow tint A soft systolic murmur was heard in the fourth interspace to the left of the sternum, otherwise, the results of the physical examination were negative The urine was of low specific gravity (1.010) Albumin, sugar and casts were not found The reaction was acid to litmus Urobilin was absent The gastric contents did not contain free hydrochloric acid At the time of admission, the analysis of the blood showed hemoglobin, 40 per cent, erythrocytes, 1,800,000, leukocytes, 5,900, polymorphonuclear neutrophils, 66 per cent, lymphocytes, 34 per cent The red cells showed moderate anisocytosis and achromia The platelets numbered 340,000 The bleeding time was four minutes and forty seconds The coagulation time was three minutes (capillary tube method) Reticulated red cells were not observed

*Diagnosis*—A diagnosis of pernicious anemia was made, and the patient was put on a liver diet and given dilute hydrochloric acid with his meals He was also given a blood transfusion of 500 cc of whole blood He was discharged on August 23, at which time the hemoglobin content was 60 per cent, erythrocytes, 3,600,000, leukocytes, 3,800, polymorphonuclear neutrophils, 52 per cent, lymphocytes, 48 per cent, and reticulated red cells, 0.8 per cent

*Course*—The patient was readmitted to the hospital on April 13, 1927 He had been observed in the outpatient department since his discharge and had been feeling well until one month previously, when he complained of nausea and vomiting after meals The vomiting had increased in frequency and amount so that he could retain nothing taken by mouth He lost about 12 pounds (5.4 Kg) One day previous to admission, he had a tingling and burning sensation in his hands, legs and feet Physical examination showed an acutely ill man, whose skin was a lemon yellow tint, and who appeared anemic His pupils reacted sluggishly on light and distance The fundi were normal A cardiac murmur was not heard at this time The analysis of the blood showed hemoglobin, 81 per cent, red blood cells, 4,000,000, leukocytes, 6,300, polymorphonuclear neutrophils, 73 per cent, and lymphocytes, 27 per cent The red cells showed slight anisocytosis, poikilocytosis and achromia The Wassermann reaction was negative The systolic blood pressure was 114, the diastolic, 84 The urine had an acid reaction to litmus The specific gravity was 1.030, there was a trace of albumin and no sugar, a few hyaline casts were noted The contents of the stomach when fasting, the test meal and the vomitus did not contain free hydrochloric acid The clinical course was as follows On April 14, the nitrogen content of the urea was found to be 52.8 mg per hundred cubic centimeters of blood The carbon dioxide combining power was 61.7 per cent The urine contained a trace of albumin and a few hyaline casts The patient seemed in good condition but continued to vomit a

large amount of green watery material. On April 22, the vomiting stopped, the nitrogen content of the urea was 55.8 mg per hundred cubic centimeters of blood, the carbon dioxide combining power was 78.7 per cent and the  $p_{\text{H}}$ , 7.6. The urine contained many hyaline and granular casts. Six days before this, he had been given a proctoclysis containing 8 Gm of sodium bicarbonate. He retained, however, only about half of the dose. The next day he received 2 Gm more by proctoclysis. On April 25, the carbon dioxide was 86 per cent by volume, the sodium chloride of the plasma, 4.15 Gm per liter, the  $p_{\text{H}}$  of the blood, 7.5, and the total chloride content of the urine, 0.6 Gm, or 0.04 per cent. On April 26, he again began to vomit. On April 30, the carbon dioxide content was 74.4 per cent by volume. The patient died the following day.

The methods used for the analyses of the blood and urine were (1) urea nitrogen, Van Slyke and Cullen, (2)  $p_{\text{H}}$  of serum, indicator phenol red, (3) carbon dioxide, Van Slyke, (4) calcium, Tisdall's modification of the method of Kramer, (5) sodium chloride of the plasma, McLean, (6) urine and total chlorides, Volhard and Arnold. Phenolphthalein was used as an indicator for acidity. The accompanying table gives the clinical course and laboratory observations in more detail.

*Pathologic Report*—The pathologic report submitted by Dr L. C. Knox was as follows. Only a restricted postmortem examination was permitted, hence, many factors of especial interest remain undetermined. As no organ could be removed the microscopic examination was limited to a small portion of one kidney. The mucosa of the stomach did not present any ulcers but was much injected. The pylorus and duodenum also were apparently free from ulcers. The surface of the liver was smooth and glistening, and the gland was of normal consistency.

The left kidney was small and the cortex nearly atrophic, owing to an old obstruction to the outlet of the pelvis and a resulting hydronephrosis. The peripheral rim of kidney tissue was about 0.5 cm thick, and the markings were lost.

The right kidney was much larger than normal and was soft. The capsule could be stripped only with some difficulty, and the cortical surface was red and granular. The parenchyma was much injected, and the markings were obscure. A diagnosis of left hydronephrosis with atrophy and of right renal hypertrophy with chronic nephritis was made.

Microscopically, the sections of the right kidney showed a slight degree of chronic interstitial nephritis, and also a superimposed lesion which we regarded as a subacute toxic nephrosis. This entirely predominated over the chronic change. The latter was slight, as shown by a diffuse penetration of hyaline connective tissue between a few groups of cortical tubules and complete hyaline sclerosis of a few glomeruli. Occasional lymphocytes were found in these scars, but there were no vascular and almost no glomerular lesions. These areas did not form the cortical wedges of new tissue seen in arteriosclerotic kidneys, but were somewhat irregular in distribution, and their extent and significance were of only minimal amount and appeared relatively unimportant.

The associated acute or subacute process was severely toxic and caused great damage to the tubular epithelium especially, though not entirely restricted to the convoluted tubules. Much necrosis was present and only a slight degree of regeneration. The cells of the convoluted tubules were frequently without nuclei, the cell walls were broken down, the cytoplasm was amorphous, rarely vacuolated or granular. The lumina of these tubules contained globular masses of cytoplasmic debris, homogeneous and not strongly acidophil. In certain tubules, there was also calcification of the necrotic cytoplasm, shown by blue staining droplets or amorphous masses sometimes within the epithelial cells and sometimes taking place in the already desquamated cells. In a few of the straight tubules it was separate

# *Chemical Course and Laboratory Observations in the Case Reported*

Date, 1927	Blood				Urine				Clinical Course
	Urea Nitrogen 28	Carbon Dioxide Combining Power, per Cent by Volume 61.7	Sodium Chloride of Plasma, Gm per Liter	Calcium, Mg per 100 Cc	Total Chlorides	Acidity, Number Cc of tenth Normal Sodium Hydroxide to Neutralize	Albumin Trace	Microscopic Observations Few hyaline casts	
April 14									In good condition, pulse rate good, vomited large amount of green fluid blood present in vomitus
April 15							Trace	Many hyaline casts	Weak, pulse of poor quality, temperature, 100 F., hypodermoclysis of 750 cc of 5 per cent dextrose given
April 16							Very faint trace	Few hyaline casts	Annie, gastric lavage given with return of light brown fluid, proctoclysis containing 8 Gm of sodium bicarbonate given, hypodermoclysis of 1,000 cc of 5 per cent dextrose given
April 18	66.9	67.3							Annie no longer present, vomited 1,000 cc given hot pack, hypodermoclysis and proctoclysis containing 4 Gm of sodium bicarbonate no longer vomiting
April 20 21	55.8	78.7	3.25				Faint trace	Many hyaline and granular casts	Given hypodermoclysis and proctoclysis containing ammonium chloride, also given dilute hydrochloric acid by mouth
April 22	66.8	96.0		7.6					Irrational, hypodermoclysis of 5 per cent dextrose given, and infusion of 500 cc of physiologic sodium chloride solution and 10 cc of calcium chloride
April 23	67.0	86.0		12.2	Too little to estimate	64			Saline and chloride given intravenously, much improved, the percentage of ammonia in the urine was 0.054, no longer vomited
April 25		86.0	4.15	7.5	0.6 Gm or 0.04% 0.10 Gm or 0.07%	26	Faint trace	Many hyaline casts	Improving, saline and calcium chloride given intravenously
April 26						52	Trace		Irrational, temperature, 101 F., general condition worse, infusion and hypodermoclysis given vomited large amount of dark green fluid
April 27		86.5		13.0					Condition worse, hypodermoclysis and infusion given, vomited only 90 cc, pulse rate rapid and weak, vomited large amount of green water
April 29	77.0	88.6	4.60		Too little to estimate	62	Trace	Many hyaline and granular casts	Continued to vomit, blood transfusion of 300 cc given, very drowsy, hypodermoclysis of 5 per cent dextrose given
April 30		74.4							Patient worse Chvostek sign positive, irrational, anuric
May 2									Temperature 106.2 F., died

from the epithelium, and the salts had the concentric rings and refractile appearance seen in old calcified lesions in other parts of the body, but more often it occurred within cells or portions of cells. The glomeruli were unaffected by this process and did not show evidence of degenerative or proliferative change but were much congested.

This lesion, therefore, had the characteristics of that seen in kidneys affected by bichloride poisoning and could not be morphologically distinguished from it. There was diffuse edema and diapedesis of red cells throughout the interstitial tissue. Neither polymorphonuclear cells nor phagocytic cells were observed.

The unusual features in the case reported are (1) the association of alkalosis with uræmia, (2) the presence of a highly acid urine with alkalosis, (3) the administration of a high purine diet, as the patient was thought to have pernicious anemia.

1 *The Association of Alkalosis with Uræmia*—In many cases of chronic nephritis with marked nitrogen retention,<sup>4</sup> acidosis is a common observation. It was frequently observed, however, especially by Brown, Eusterman, Hartman and Rowntree,<sup>5</sup> and by Palmer and Henderson,<sup>6</sup> that nephritis is produced by alkalosis, and that many of the toxic symptoms of alkalosis are due to the accompanying nephritis. That the administration of alkali in cases of nephritis is dangerous has been shown by many observers. Instances were reported by Howland and Marriot,<sup>7</sup> Morse,<sup>8</sup> Harrop,<sup>9</sup> and Sellards.<sup>10</sup> This patient received about 6 Gm of sodium bicarbonate by rectum during his first three days in the hospital, and it was not thought that this would be enough to affect him. He did not have fever. He did, however, vomit. It is interesting to note that the alkalosis was most marked several days after the vomiting had ceased, and a week after the sodium bicarbonate had been administered. Moreover, when he did vomit he did not lose hydrochloric acid, for there was none in the vomitus. Three examinations, on different days, failed to reveal any free hydrochloric acid. It may be possible that the sodium bicarbonate had a prolonged effect. Goldblatt<sup>11</sup> showed that the urine remains

4 Chace, A. F., and Meyers, V. C. Acidosis in Nephrosis, *J. A. M. A.* **74**: 641 (March 6) 1920.

5 Brown, G. E., Eusterman, G. B., Hartman, H. R., and Rowntree, L. G. Toxic Nephritis in Pyloric and Duodenal Obstruction, Renal Insufficiency Complicating Gastric Tetany, *Arch. Int. Med.* **32**: 425 (Sept.) 1923.

6 Palmer, W. W., and Henderson, L. J. Clinical Studies on Acid-Base Equilibrium and the Nature of Acidosis, *Arch. Int. Med.* **12**: 153 (Aug.) 1913.

7 Howland, John, and Marriot, W. M. *Quart. J. Med.* **11**: 289, 1918.

8 Morse, J. L. *New York M. J.* **112**: 965, 1920.

9 Harrop, G. A. J. *Bull. Johns Hopkins Hosp.* **30**: 62, 1919.

10 Sellards, A. W. *Bull. Johns Hopkins Hosp.* **23**: 289, 1913, *ibid.* **25**: 141, 1914.

11 Goldblatt, M. W. *J. Biol. Chem.* **21**: 991, 1927.

alkaline for several days after the administration of alkali, but in all cases he gave a much larger dose of alkali and not in any case did the urine remain alkaline for as long as a week

2 *The Presence of a Highly Acid Urine with Alkalosis*—An explanation of the fact may be due to

(a) A failure to excrete alkali

(b) A selective excretion of inorganic acid, thus producing a disproportional acid-base balance in the blood

(c) An overexcretion of acid and carbon dioxide by the lungs. This could not have been present in the case reported, as hyperpnea was absent

(d) A loss of acid metabolites by vomiting. This condition did not exist in our patient at the height of the alkalosis. Moreover, Haden and Orr<sup>12</sup> stated, with good experimental evidence, that it is unlikely that the loss of chlorides by vomiting is the cause of alkalosis

(e) An excretion of organic acids by the kidney. Unfortunately, in the case under discussion, the organic acids of the urine were not determined. In the case reported by Harrison and Perlzweig,<sup>3</sup> diacetic acid was found in the urine. Koehler<sup>13</sup> also stated that acetone bodies may occur in the urine in alkalosis. In many diseases when the number of chlorides of the blood or urine is low, as in diabetes,<sup>14</sup> eclampsia<sup>15</sup> and pneumonia,<sup>16</sup> the organic acids are increased in the blood or in the urine, or in both. A similar process may be present in alkalosis. In pneumonia, Holten<sup>17</sup> found that at the time of the crisis when the chlorides return the glycuronic acid disappears from the urine. He suggested that the retention is due to the formation of acids which stimulate the tissues in some way to retain chlorides.

Acid urine associated with alkalosis has been noted by many observers. Hariop<sup>9</sup> stated that normally 5 Gm. of sodium bicarbonate will produce alkaline urine, yet in other cases 50 Gm. will not produce a basic reaction in the urine. Sellards<sup>10</sup> reported that in the chronic parenchymatous types of nephritis sodium bicarbonate is easily excreted, while in the acute nephritic types with typical uremia it is excreted with difficulty.

12 Haden, R. L., and Orr, T. G. *J. Exper. Med.* **37** 365, 1923

13 Koehler (footnote 2, second reference)

14 Gram, H. C. *J. Biol. Chem.* **56** 593, 1923

15 Williams, J. W. *Obstetrics*, New York, D. Appleton & Company, 1923, p. 604. Stander, H. J., and Radelet, A. H. *Bull. Johns Hopkins Hosp.* **38** 423, 1926

16 Medigreanu, F. *J. Exper. Med.* **18** 259, 1913. Holten, C. The Formation of Organic Acids and the Retention of Chlorides in Lobar Pneumonia, *Arch. Int. Med.* **38** 489 (Oct.) 1926

17 Holten (footnote 16, second reference)

3 *The Administration of a High Purine Diet, as the Patient was Thought to Have Pernicious Anemia*—The pathologic picture in this case is one of toxic nephrosis which we believe to be caused by the increasing  $p_{\text{H}}$  of the tissues, and it seems probable that a sort of vicious circle is set up because the kidney holds back the alkaline metabolites and excretes those which are acid

This case differs from the one reported by Harrison and Perlzweig in that the plasma bicarbonate content in their case was only slightly elevated, while in our case it was very high. Van Slyke<sup>1</sup> pointed out that the bicarbonate content of the plasma is not an infallible guide to the hydrogen ion concentration

#### COMMENT

Harrison and Perlzweig mentioned the possible causation of alkalosis by nephritis. The clinical and pathologic picture in the case reported is one of a toxic nephrosis—a condition which has been observed to be associated with alkalosis and indeed seems to result from it.<sup>18</sup> The pathologic observation is of considerable interest for the reason that only a few fatal clinical cases of alkalosis have been described, and fewer have been examined post mortem. The renal changes conform morphologically to those occasionally described in patients who die from pyloric obstruction, with or without tetany. Renal lesions in tetany were described first in one case by Nazzari,<sup>19</sup> in six cases by Brown, Eusterman, Hartman and Rowntree,<sup>5</sup> in four by Zeman, Friedman and Mann,<sup>20</sup> and in one by Knox.<sup>21</sup> For few of these patients were as complete chemical examinations of the blood made as would now be deemed desirable, but there is little doubt that the lesions observed by these authors were practically identical and were associated with alkalosis.

Interest has naturally been focused on the etiology of the lesion, its resemblance to the bichloride nephrosis, and its relation to or dependence on a preexisting inflammatory lesion of the kidney. The etiology of such a condition is discussed elsewhere in this paper. The question of producing a renal lesion similar to the nephrosis of bichloride poisoning by any other agent has been answered by Fahr,<sup>22</sup> who

18 Zeman, F. D., Friedman, W., and Mann, L. T. *Proc. New York Path. Soc.* **24** 41, 1924. Brown, Eusterman, Hartman and Rowntree (footnote 5). Stieglitz, E. J. *Alkalis and Renal Injury*, *Arch. Int. Med.* **41** 10 (Jan.) 1928.

19 Nazzari, Alessio. *Alterazioni renali nella tetania gastrica*, *Policlinico*, 1904.

20 Zeman, Friedman and Mann (footnote 18, first reference).

21 Knox, L. C. *Proc. New York Path. Soc.* **24** 41, 1924.

22 Fahr, T. *Pathologische Anatomie der Morbus Brightii*, in Henke and Lubarsch. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1925, vol. 6.

admitted that the changes caused by mercury are not specific but are so highly characteristic as to justify the title of a sublimate necrosis

Necrotic nephroses may also occur in dysentery, cholera, diphtheria, malaria, typhus and diabetes, but calcification of the tubular epithelium is not described in these diseases. Lubarsch<sup>23</sup> observed necrosis with calcification twice in phosphorous and once in morphine poisoning. Other chemical poisons resulting in necrosis, as chromium, uranium, hydrochloric and sulphuric acid, do not show the regeneration and calcification observed in sublimate poisoning. Oxalic acid caused calcification, but of the exudate only, and not within the epithelial cells. Calcification is believed to be dependent not only on the duration of the renal necrosis but also on the severity, as it may occur in seven days with a massive dose of bichloride, and with smaller, but fatal, doses, it may be absent. The duration of the alkalosis in these cases can scarcely be determined. In some patients it has preceded and in some followed anesthesia, and hence may develop without the addition of another chemical irritant. The patients described by Brown and his associates had symptoms varying from six months to twenty years, and calcification was observed in the kidneys of both the patients. The duration of the toxic agent is, therefore, probably unimportant.

The question of the rôle played by the accompanying nephritis is difficult in the face of such scanty observations. In the paper from the Mayo Clinic,<sup>5</sup> five of the six kidneys described show, we believe, essentially, the morphology revealed in figure 2. Although they are classified by the authors as "acute toxic nephritis," in only one of them were there glomerular lesions, two others showed slight diffuse fibrosis and a few lymphocytes. Apparently, the authors regarded the lesions as more toxic than inflammatory. This, also, was the view held by Bach and Mann,<sup>24</sup> whose experimental work on cats tended to support this belief.

The patient described, although having diminished renal tissue due to the hydronephrotic and atrophic left kidney, presented an extensive acute lesion in the right kidney, essentially toxic and degenerative, the result of other factors than the slight chronic inflammation present in the kidney at the same time.

The absence of pyloric or duodenal obstruction is noteworthy and indicates that the toxic state has causes other than the mechanical ones, which have so generally been found. It is possible that chemical or bacterial poisons unknown to us were responsible for the renal damage.

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23 Henke and Lubarsch. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1925, p. 221.

24 Bach, G. *Proc. New York Path. Soc.* **24**: 41, 1924.

In the case under discussion, other reasons for uncompensated alkali excess, such as the administration of alkali, the loss of acid metabolites by vomiting, fever and hot bathing, are not present. It is difficult to account for the source of the alkaline metabolites in the blood, unless it is the result of a deranged metabolism occurring in a case of pernicious anemia in which the products of catabolism are alkaline rather than acid as is usually the case. Moreover, in this case, there was only one kidney, and the presence of an alkalosis associated

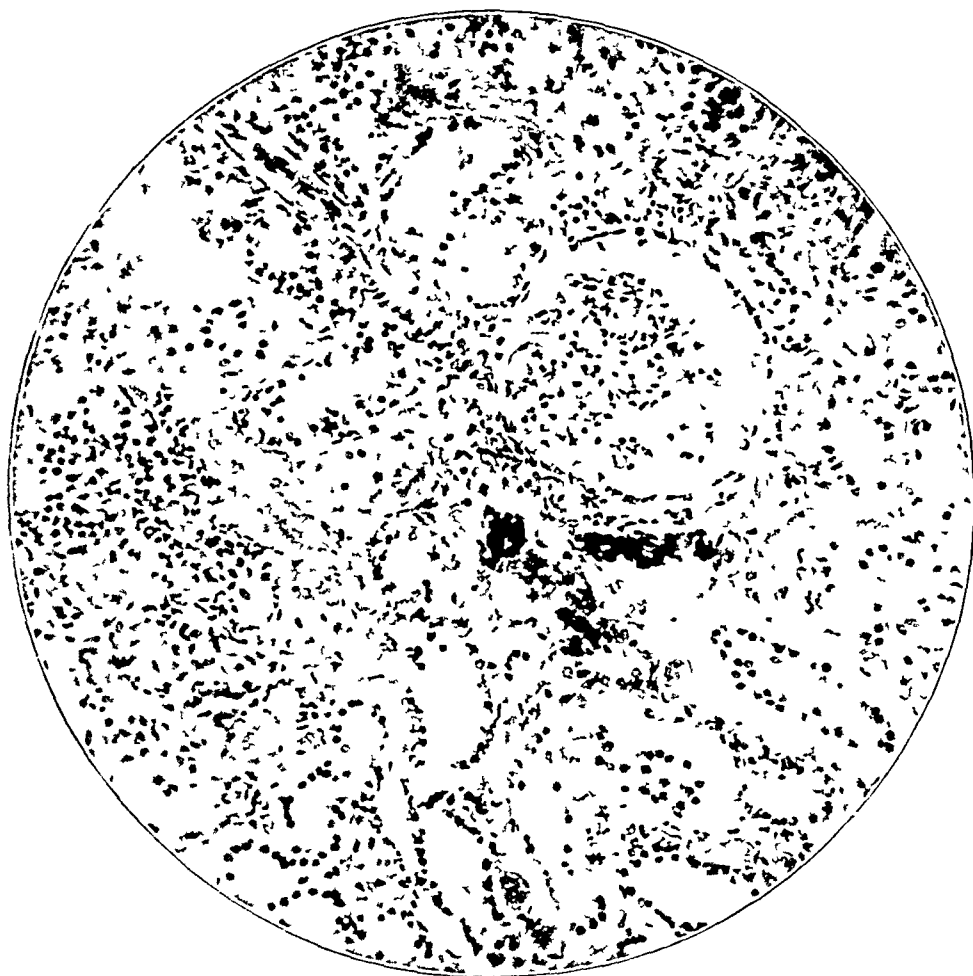


Fig. 2—Photomicrograph showing the renal lesion in the case of alkalosis

with a high purine diet may have resulted in the functional disturbance of the one good kidney, so that it was unable to excrete the alkaline metabolites, and thus a severe alkalosis was produced.

Van Slyke and Palmer<sup>25</sup> showed that in normal men the urine becomes more alkaline than the blood ( $p_H=7.4$ ) when the carbon dioxide of the plasma bicarbonate exceeds  $71 \pm 5$  per cent by volume. They also stated that in most of the pathologic cases studied the urine

25 Palmer, W. W., and Van Slyke, D. D. *J. Biol. Chem.* **32**: 499, 1917.



did not become more alkaline than the blood until a higher bicarbonate content of the plasma had been reached than in normal persons. Hence, it would seem that it is easier for a normal kidney to excrete alkaline than acid metabolites, however, when the kidney is damaged, the reverse may be true.

In acute nephritis, it has been found that little if any ammonia<sup>26</sup> is excreted in the urine. This may, in part, account for the low  $p_H$  of the urine. Van Slyke and his associates<sup>26</sup> stated that in spite of the low ammonia content in the glomerular nephritides, if the titratable acid remains at about the normal level, acidosis may be, and frequently is, absent. We will go a step further and say that not only may acidosis be absent, but alkalosis may be present.

In the patient described, the chloride content of the blood was low, and there was practically no chloride in the urine, although he had been receiving sodium chloride, ammonium chloride and calcium chloride by mouth, by rectum, subcutaneously and intravenously.

In experimental alkalosis, it has been found that even though chlorides are absent in the urine, the stomach<sup>11</sup> continues to secrete hydrochloric acid normally, in the case reported, however, even this was not observed. Perhaps, as Haden and Orr<sup>12</sup> believed, the chlorides are fixed by toxic substances in the blood for the purpose of neutralization. It is not improbable that it may be the function of the chlorides to maintain the acid base equilibrium of the tissue, and so they are retained. That there is a disturbance of carbohydrate metabolism in alkalosis has been shown by Goldblatt,<sup>11</sup> who reported that there is a definite diminution in carbohydrate tolerance and that frequently ketone bodies appear in the urine of dogs on which the experiments were performed. Lactic acid in the urine is also increased. It may be possible in a condition in which the carbohydrate metabolism is deranged and organic acids are formed and excreted that the chlorides are retained to maintain the acid base balance.

It hardly seems probable that the chlorides are retained, because the renal threshold for chloride is high. In this event, one would expect the chloride content of the blood to be increased.

When one calculates the millimolecular concentration of the anion and cation, it is found that there is a loss of basic as well as of acid metabolites. An exact determination of the millimols could not be made in our case because of an insufficient amount of data. The chlorides, however, were found to be 58 millimols, the carbon dioxide was 35.1 millimols and, assuming a high normal for organic acids and proteins, the total acid metabolites could not exceed 135

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<sup>26</sup> Van Slyke, D. D., Linder, G. C., Hiller, Alma, Leiter, L. and McIntosh, J. F. *J. Clin. Investigation* 2: 255, 1926.

millimols, hence, the total base could not exceed this amount, for the two must be equal. On the other hand, if the organic acids are high, the foregoing statement would be invalid, and there would not be any loss of basic radicals. If there is a loss of base, it may be possible that some of the chloride is bound by the basic radicals and distributed in the tissues in the form of an imperceptible edema.

In many previously reported cases of alkalosis,<sup>27</sup> the association of nephritis with the condition has been noticed, however, it has not been considered the cause of the condition, but rather the result of the alkalosis. It is well known that the kidney has a selective excretory function, a common clinical observation is a kidney which can excrete salt and dyes and not nitrogenous substances, and vice versa. While nothing is known of the selective alkali excretion of the kidney, there is not an inherent improbability in the assumption, however, in view of the pathologic observations in the case reported and in others,<sup>28</sup> it seems more likely that the renal lesion is the result of the alkalosis. The presence of nephritis or nephrosis might account for the continuation of an alkalosis when once produced, but it is difficult to account for the origin of the alkalosis unless it is that in this case the catabolism resulted in alkaline metabolites rather than in acid end-products.

#### SUMMARY

A case of alkalosis occurring in the presence of anemia is described. The peculiar features of the case are the association of an alkalosis with uremia, the presence of a highly acid urine with alkalosis and the fact that the patient had been on a high purine diet and had been given free hydrochloric acid with his meals. Moreover, autopsy revealed that he had only one functioning kidney, which was damaged. It is not believed that either the vomiting or the small amount of sodium bicarbonate that was administered could cause the alkalosis.

#### CONCLUSION

The high  $p_{\text{H}}$  in this case probably resulted from the formation of basic end-products, and the deranged catabolic process was in some way dependent on the pernicious anemia. It seems unlikely that the alkalosis in this instance was the result of either the vomiting or the administration of sodium bicarbonate.

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27 Chace and Meyers (footnote 4) Stieglitz (footnote 18, third reference)

28 Brown, Eusterman, Hartman and Rowntree (footnote 5) Zeman, Friedman and Mann (footnote 18, first reference)

# BRONCHOGENIC SQUAMOUS CELL CARCINOMA

REPORT OF A CASE ASSOCIATED WITH PLEURAL EFFUSION AND  
PULMONARY OSTEO-ARTHROPATHY, WITH FEATURES THAT  
SIMULATED INFECTION BY *ENDAMEBA HISTOLYTICA* <sup>\*</sup>

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Infections by *Endameba histolytica* are assuming more and more importance in the medical practice of the United States, and the literature of today contains frequent references to supposed cases of extra-intestinal lesions caused by this parasite. Doubtless some of these cases are genuine, but the impression is growing that a mistake in diagnosis is responsible for a great many. Most of these reports are written by pathologists who are unfamiliar with protozoology, or by protozoologists who do not appreciate the bizarre forms that human cells may assume under pathologic conditions, or even by those who are neither pathologists nor protozoologists. The case reported in this article represents some difficulties in diagnosis, and the observations may be of value to those similarly confronted.

## REPORT OF CASE

*History*—A woman, aged 54, of Greenville, N. M., was admitted to the Colorado General Hospital on Nov. 29, 1925. She had contracted typhoid fever at the age of 6, pneumonia at 13 and influenza one year previous to her entrance to the hospital. At the age of 17 she had night sweats "due to goiter." In recent years, she had undergone occasional attacks of pleurisy. She had had frequent sick headaches associated with gastric symptoms. Her skin had become extremely yellow ten months and six months previous to presentation. She had always been constipated. The chief complaints were as follows: pain in all the joints of the extremities, weakness, swelling of the feet and hands, cough, vomiting following coughing spells, loss of weight and a sensation of heaviness across the chest. At the time of admission to the hospital there had been pain in the knees for three years, but it had not been severe until the last six months. Finally, the pain had spread to all the joints of the extremities. Weakness was then marked. There had not been any fever. Swelling of the feet and knees had been noted three months before, and swelling of the hands had been present for the last five weeks. A bronchial cough had been troublesome for years, but it had been much worse for the last six months. The total loss of weight was 35 pounds (15.9 Kg.), of which 25 (11.3 Kg.) had been lost during the last three months. The sensation of heaviness across the chest had begun three months before.

<sup>\*</sup> Submitted for publication, Nov. 7, 1928.

<sup>\*</sup> From the Section on Pathologic Anatomy, The Mayo Clinic, Rochester, Minn.

*Physical Examination*—General examination disclosed marked emaciation, muscular atrophy, marked weakness, excessive coughing and sallow and slightly brownish skin. The patient was intelligent and cooperative. The supraclavicular lymph nodes on both sides were palpable and tender. The hands, wrists and fingers were swollen, and the muscles of the arms were atrophied. The hand grips were weak but equal. Dulness was noted over the lower lobe of the right lung, anteriorly, and vocal fremitus was much increased over the right apex. Numerous inspiratory rales were noted over the left base, posteriorly. The skin over the abdomen was inelastic. Tenderness was elicited in the right upper quadrant and the liver was palpable below the costal margin. The knee jerks and other reflexes were active. There was voluntary spasticity of the various muscles. The clinical course of the case, with results of laboratory examinations, can best be followed chronologically.

*Laboratory Examinations*—On Nov. 30, 1925, the urine did not contain anything abnormal with the exception of numerous threads of mucus. The hemo-

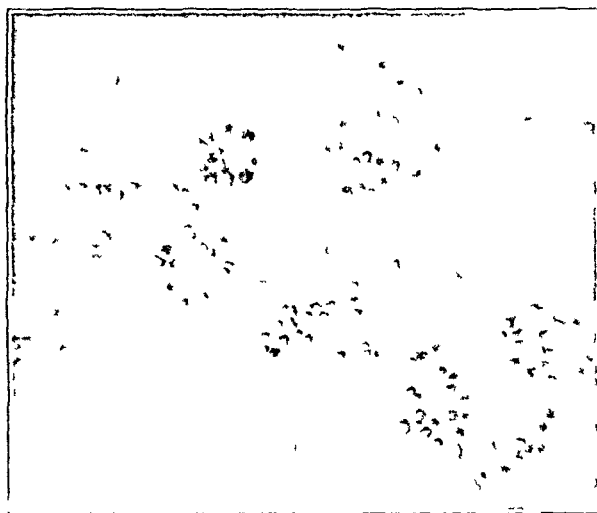


Fig. 1—Ameba-like cells from the pleuritic fluid, in active motion. There are several relatively sharp pointed pseudopodia for each cell. Hyaline refractive bodies are found in the cytoplasm, even well out into the pseudopodia. These are probably fat droplets. One nucleus is distinctly outlined. There are no vacuoles. (Photograph by Dr. Hugh M. Kingery,  $\times 650$ )

globin was 74 per cent. Erythrocytes numbered 4,600,000 and leukocytes 16,000 per cubic millimeter. Eighty-six per cent of the leukocytes were polymorphonuclear neutrophils. On Dec. 1, 1925, pain was noted in the right side of the chest, in the midaxillary line, especially on coughing. There were no physical signs to explain this pain. There was a marked rise in temperature. The number of leukocytes rose to 22,230 per cubic millimeter. The Wassermann test was negative. On December 3, 30 cc of turbid, flaky fluid was withdrawn from the right pleural cavity. The fluid was not bloody, it contained "ameba-like cells" which occurred in pure culture, travelled across the field rather rapidly and thrust out sharp pseudopodia. A nucleus was to be seen in a few of them, but rather indistinctly. Bacteria were not found in this fluid. Erythrocytes from a human being were added to the culture in a test tube, and were engulfed in small numbers. These ameba-like cells remained alive in the cultures for three weeks (fig. 1).

*Special Examinations*—Examinations with special apparatus were now indicated, and on December 4 roentgenograms were made. The lower third of the right lung was obscured by an area of rather homogeneous density which was shown, by shifting the patient's position, to be attributable to the presence of fluid (fig 2). A separate shadow at the hilum was thought to be a tumor. There was increased fibrosis and peribronchial thickening throughout the entire bronchial system, with fibrotic and partly calcified lymph nodes and strands radiating from the hilum. The heart appeared normal, but the right border could not be outlined. The liver was normal. The left kidney was smaller than the right. The spine was normal. Periosteal changes and spurs were noted in the

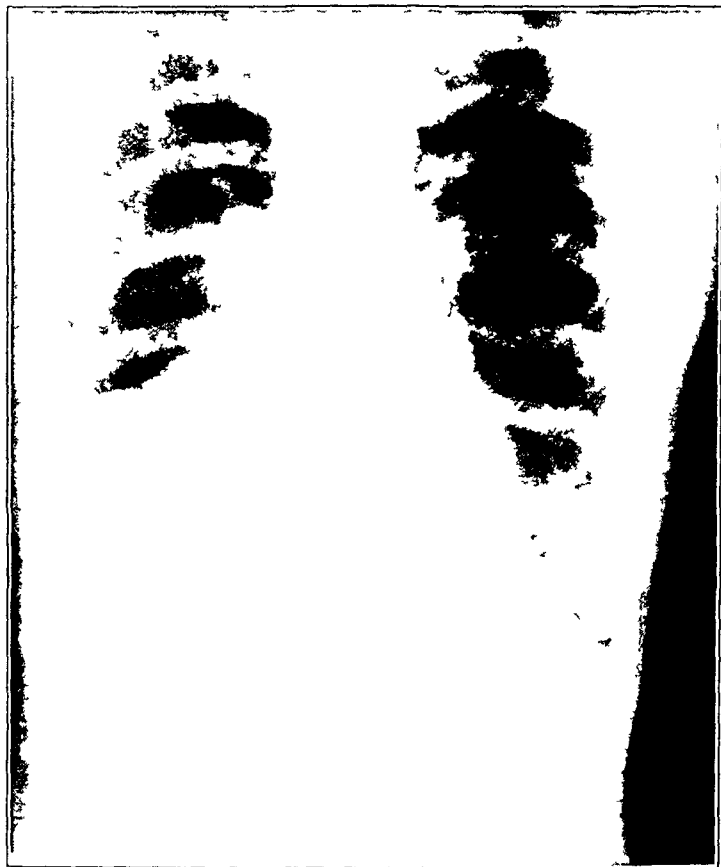


Fig 2—Roentgenogram of the chest, showing fluid in the right pleural cavity. The shadow blends with that of the right border of the heart. The shadows about the hilum were suspected to be those from a malignant growth.

heels. An extensive lacework-type of periosteal change of both tibiae and fibulae (fig 3), less marked in the metatarsals, was present. The ankle joints appeared clear. The knee joints gave the appearance of synovial thickening, such as is found in villous arthritis. There were no bony or cartilaginous changes. The same type of periosteal thickening was found in the metacarpals and phalanges, as well as in each radius and ulna (fig 4). This periostitis was not syphilitic in type but resembled more closely pulmonary osteo-arthritis. Cystoscopy performed on December 5 revealed a normal bladder and normal ureters. The urine, obtained by ureteral catheterization, was sterile. There was marked delay

in phenolsulphonphthalein excretion from the right kidney. Amebas were not found in the feces either by the warm-stage method or by the iron hematoxylin stain.

Various expedients were tried during the next six or seven weeks in the hope of arriving at a definite diagnosis and helping the patient. On December 12 a specimen of sputum was found to contain ameba-like cells. The leukocytes, on December 8 numbered 83,000.

On December 11 a pyelogram showed enlargement of the pelvis of the right kidney, and a shadow suggested the presence of a calculus. The kidney was

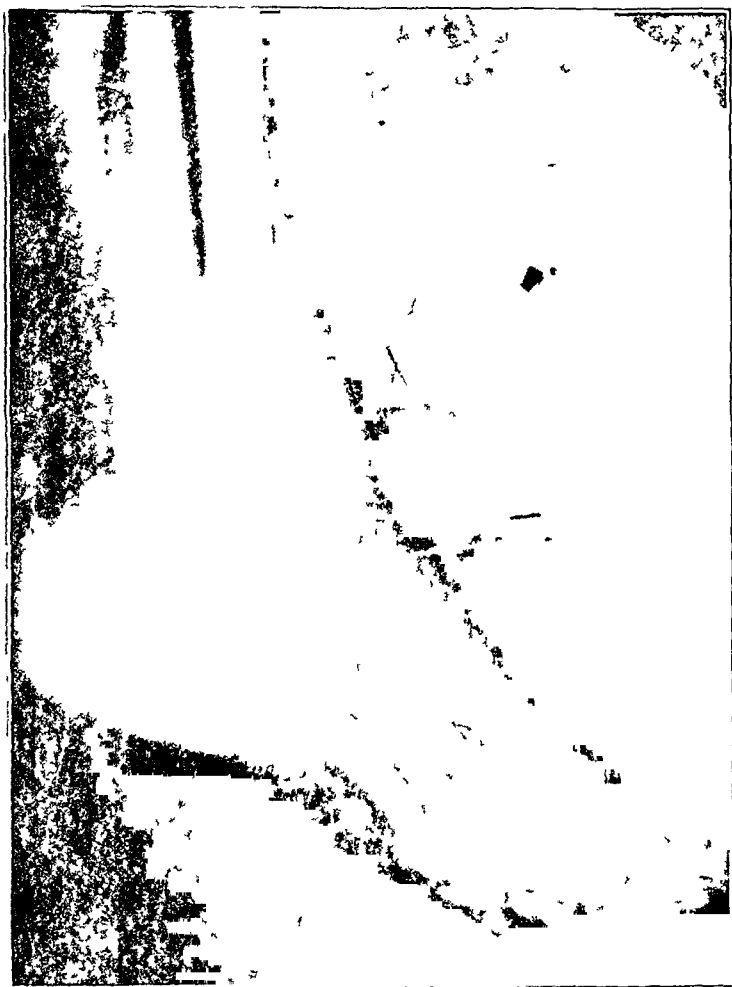


Fig. 3—Roentgenogram of the foot. Periosteal thickening of the lower end of the tibia and fibula, and to a lesser extent, of the metatarsals is noted. There is a spur on the os calcis.

displaced downward. Thoracentesis of the right side of the chest was performed on December 12, when 15 cc of a turbid fluid was withdrawn. When the fluid stood, a gelatinous clot formed. Ameba-like cells were present in large clumps. In the warm incubator, these moved out freely. They measured from 25 to 30 micromillimeters in diameter.

*Treatment and Subsequent Course*—Following this examination, treatment with emetine was begun on December 13, and the general condition of the patient improved rapidly. The sputum contained ameba-like cells. The urine contained

ameba-like cells which were from 5 to 15 micromillimeters in diameter, as well as organisms found to be *Trichomonas vaginalis*. The patient was much more comfortable by the night of December 14. The hemoglobin on that day was 60 per cent, the erythrocytes numbered 3,100,000 and there were 77,000 leukocytes, of which 71 per cent were polymorphonuclear neutrophils. On December 17, the sputum contained ameba-like cells, but none was found in the feces. There was continued improvement until December 20, but indurated areas developed in the arms from the injections of emetine. A roentgenogram of the chest was made on December 24, after partial aspiration of 400 cc of effusion (fig 5). There was



Fig 4—Roentgenogram of the hands. Periosteal thickening of the radius, ulna, metacarpals and phalanges is noted. The wrist joint is apparently free.

still uncertainty as to the nature of the condition in the region of the right lung, the diaphragm and the liver. The condition of the hands and feet remained unchanged. The stomach and gallbladder appeared normal. After an interval of four days, the treatment with emetine was resumed on December 27. The patient felt better and slept soundly. The cough was markedly lessened. On December 31, the condition of the lung had not changed. Deep roentgen treatment was instituted. By Jan 6, 1926, local results were not observed from the roentgen treatments, but there was improvement in the general condition. An examination, from the orthopedic standpoint, was made on January 6. Both arms were tender to passive motion. The right elbow lacked 15 per cent of full extension, and

the left 25 per cent. There was limitation of motion in the wrists and phalanges, and slight synovitis of the affected joints. It was felt that the periostitis was caused by absorption from some infection.

On January 7, various examinations were repeated. The hemoglobin was 75 per cent. The erythrocyte count was 4,170,000, the leukocyte count, 16,700, and of the leukocytes 75 per cent were polymorphonuclear neutrophils. Bacilli of tuberculosis were not found in the sputum. Examination of the pleuritic fluid showed that it was hazy, that it contained numerous white flakes and that it was sterile. On the warm stage were seen large nonmotile cells of uncertain type. Some of the smaller cells measured about 15 micromillimeters in diameter.

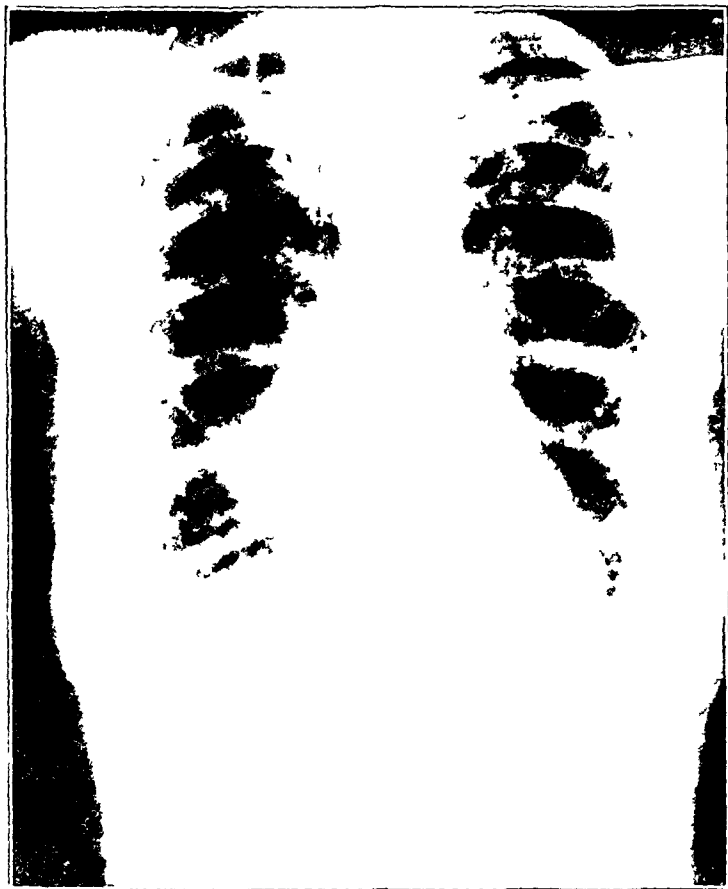


Fig 5—Roentgenogram of the chest after withdrawal of considerable fluid. The sharply demarcated shadow in the right side of the chest is believed to indicate a malignant tumor and an area of consolidation of the lung lying nearer the wall of the chest.

Many cells, both large and small, showed long projections. A hematoxylin and eosin stain of the sediment showed the nuclei to be round or oval, some stained heavily and others lightly. Mitotic figures were not seen. The large cells measured as much as 25 micromillimeters in diameter. The question of a malignant condition was raised. An occasional erythrocyte and once in a while a polymorphonuclear neutrophil were seen. This specimen was examined several hours after withdrawal and after it had been allowed to cool.

By January 13, some difficulty in swallowing had developed. Accordingly, on December 14, a roentgenogram was made of the esophagus. Opposite the bifur-



cation of the trachea was noted a constriction which was conical in shape, with the apex pointing downward. A malignant condition was suspected (fig 6). Esophagoscopy did not reveal involvement of the mucosa.

On January 25, the patient was dismissed from the hospital at her own request, and unimproved in most respects. The diagnosis on dismissal was malignant growth of unknown nature in the mediastinum, and pleuritis of the right side of unknown etiology. She was admitted the same day to the Woman's Hospital, Denver. Biopsy of a cervical lymph node was made (Mumey) on January 26. From this the diagnosis of carcinoma was made (Mills).

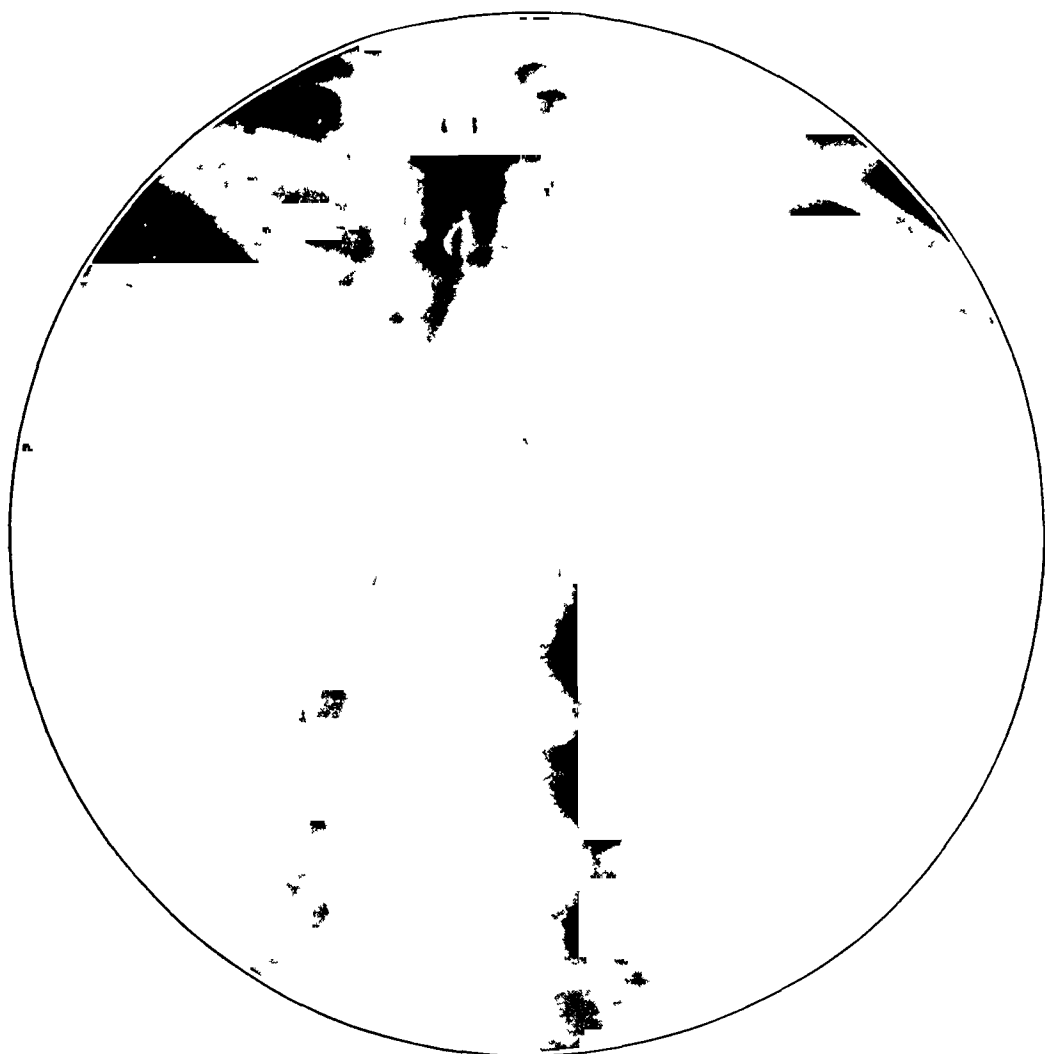


Fig 6—Roentgenogram of the esophagus containing contrast medium. The conical dilatation is due to stricture below, the result of pressure from the left side.

The patient became progressively worse and suffered from increasing difficulty in swallowing and oppression in the chest. She died at 9 p. m. on January 29. Necropsy was performed at 10:30 p. m. (Mills).

*Postmortem Examination*—Postmortem examination showed, externally, irregular masses of lymph nodes above the clavicle. The joints in various parts of the body were enlarged and irregular in outline. The bones of the hands and fingers were definitely enlarged, and the tips of the fingers were clubbed. The

knees were greatly enlarged. The left ankle creaked on passive motion. The toes were not as large, relatively, as the fingers.

Within the abdominal cavity were numerous lax fibrous adhesions which were especially noticeable between the dome of the liver and the adjacent part of the diaphragm. The small scars or thickenings of the capsule of the liver had no counterpart on section of the organ, which was normal in all respects. The gallbladder contained two irregular, faceted, grayish-brown stones.

The left kidney was normal in size and appearance, whereas the right was somewhat enlarged and had a distended pelvis in which lay a soft, friable, irregularly-shaped stone, measuring 3 cm. in the longest dimension and 0.5 cm. in the shortest dimension. The calices were thickened, but there was no definite change in the cortex or medulla. The wall of the pelvis was somewhat thickened, and the surface was irregular and somewhat hyperemic. The corresponding ureter was likewise thickened and inflamed.

Abnormalities were not discovered in the gastro-intestinal tract except that the esophagus was adherent to the surface of the mediastinal tumor just below the bifurcation of the trachea. The mucosa was freely movable in spite of the fixation of the external layers. Abnormalities were not found in the following organs and structures: vascular system, spleen, suprarenal glands, bladder and female genitalia.

In the thorax no trace of thymus was found. The pericardial cavity was normal. There were about 600 cc. of cloudy, yellow fluid in the right pleural cavity which, on standing, formed a yellowish flocculent precipitate. The left side of the chest was free from fluid. There were numerous lax, fibrous adhesions which bound the apex of the left lung to the wall of the chest. A hard mass was felt at the root of the lungs extending along the vessels into both lungs, particularly into the right. Firm nodules were noted in this region, lying under the pleura, but completely covered by it. The upper lobe of the right lung was essentially free from tumorous involvement, there was one small nodule in the posterior free margin. The anterior portions of the lung were free from fluid and were essentially normal, but the posterior portions were soggy and edematous. Near the apex were two or three small, calcified nodules, which represented healed tuberculous lesions. The middle lobe was almost entirely occupied by a mass of tumorous tissue measuring about 6 cm. in diameter. The outline, after incision, was found to be irregular, and sharply demarcated from the adjacent lung tissue. The neoplastic tissue was pinkish and of relatively uniform consistency and coloration. It had been little affected by hemorrhagic infiltration (fig. 7). The adjacent lung tissue was definitely compressed, but was not filled with fluid. This lobe was attached to the lower one by a number of lax, fibrous bands. The lower lobe was completely consolidated, but there were few tumorous nodules in it. The material filling the alveoli and bronchi was unusually gelatinous and spongy (fig. 8). Mucus strung out of the air cells and from the smaller bronchi. The mucus was brownish, resembling that found in the stools from patients with amebic dysentery. The pleura was not obviously involved and was smooth and glistening. The bronchi were free from obstruction.

The left lung was almost entirely free from neoplastic tissue and was not consolidated by the presence of any mucoid material. There were numerous adhesions between the lobes.

In the anterior mediastinum, about the roots of the lungs, were hard masses, which on section were found to be composed of the same sort of tumorous tissue as that previously described. It appeared to involve the lymph nodes in the vicinity, and also to form separate masses in which anthracosis was not seen.

This was more apparent on the left side than on the right. In this region, there was no encroachment on either blood vessels or bronchi. The tumor extended upward, and at the bifurcation of the bronchus, perforated the wall, producing a grayish area of necrotic material that protruded slightly into the lumen. In the adjacent portions of the bronchus, the wall was markedly infiltrated. Above this point the various lymph nodes were all enlarged, and those above the



Fig 7—Gross specimen of the organs of the chest viewed from behind. The right lung has been split open to show the spread of the tumor. The invasion of the peribronchial lymph nodes, the involvement of the bronchus, and the attachment to the wall of the esophagus may be seen. The liver, attached to a portion of the diaphragm, is shown below. The area of mucoid infiltration was taken from the lower portion of the right lung, where the dense shadow is seen.



Fig 8—Area of mucoid infiltration from the lower lobe of the right lung. The bronchi appeared as if injected with gelatin. The entire lung in this area was devoid of air and completely consolidated. Tumor cells were not found in this region, nor did these bronchi come into intimate contact with the tumorous mass in the hilum.

clavicle were still larger, some measuring 25 cm in diameter. These were somewhat harder than those lower down, and contained less coal pigment.

The anatomic diagnosis was squamous cell carcinoma of the right bronchus, with extension to the adjacent lung, the regional lymph nodes, the anterior mediastinum and the thyroid gland, with perforation of the bronchus and displacement of the esophagus, mucoid infiltration of the right lower lobe of the lung, hydrothorax in the right pleura (600 cc), chronic bronchitis, and bronchopneumonia, periosteal proliferation of the skeleton (pulmonary osteo-arthritis), cholecystitis and cholelithiasis (two stones), nephrolithiasis (right) and pyelitis, infarction of the right kidney, multiple peritoneal adhesions especially between the liver and diaphragm, healed tuberculosis of the lung (calcified tubercles) and hilum nodes with multiple pleural adhesions and emaciation.

*Microscopic Examination*—On microscopic examination, the heart, pancreas and suprarenal glands were found to be normal. In the spleen was marked endarteritis and hyalinization of the walls of the blood vessels, many of which were almost closed. The malpighian bodies were distinct and normal. There was much blood pigment in the reticulum cells of the pulp. There was slight swelling and granular degeneration of the epithelium of the proximal convoluted tubules of the kidneys. The cells of the liver appeared normal except for an occasional large droplet of fat. There were occasional collections of cells including degenerated nuclei, possibly of leukocytic origin, and a few lymphocytes and histiocytes, but the cells were not recognizable as amebas. The adjacent cells of the liver showed marked degenerative changes. The capsule was thickened, and here and there was attached to the diaphragm by bands of fibrous tissue. There were no scars beneath the points of attachment. The diaphragm was normal.

The mucosa of the bronchi was everywhere intact except at one point which is to be described. There was considerable purulent material attached to the walls, and an occasional ameba-like cell was to be seen in it. The submucous tissue was heavily infiltrated with lymphocytes, histiocytes and a few leukocytes. Amebas were not seen. The infiltration involved the peribronchial nodes and surrounding fascia. Masses of tumor cells filled the lymphatics. At one point the epithelium was broken, and the surface was slightly raised. Columns of cells passed from this point deep into the tissue, and blended with the carcinomatous material below. It was believed that the malignant growth took origin at this point, but the possibility of secondary involvement could not be excluded. The columns of cancer cells swept abruptly into the adjacent lymphatics and spread up and down inside the cartilaginous rings. The cells of the bronchial epithelium were definitely smaller and less heavily stained than those composing the carcinoma.

Microscopic examination of the malignant growth showed its spread by way of the lymphatics in the form of strings, bands, columns and irregular masses. The adjacent structures suffered degeneration as though by pressure. The nuclei of the cells were oval or elliptic, and extremely variable in size, ranging from a minimum of 10 micromillimeters through an average of 15 to 20 micromillimeters, and many of great size reached fully 100 micromillimeters in diameter. The largest nuclei were often of irregular shape, and often were stained deeply. These, as well as many others, showed various stages of degeneration. Mitotic figures were numerous, and the forms often were bizarre. Inclusion bodies also were numerous. Some were inside the nucleus or cell, others of similar appearance lay outside and, when large, had a superficial resemblance to Hassall's corpuscles. They were devoid of definite or constant structure, which suggested that they

had been formed from degenerated material that had become hyalinized and compressed. They always stained red. Remnants of bronchial glands were occasionally seen. The tumorous masses had a decided tendency to degenerate centrally when they had reached considerable size. They remained attached together so that there were no free cancer cells in the alveoli, or in the bronchus, where this was involved. Evidence of the tissue reaction provoked by invasion consisted chiefly of the presence of epithelioid cells, some lymphocytes and an occasional leukocyte. Where the muscular tissues in the neck were invaded, the fibers were separated by appreciable intervals in which was found loose tissue containing numbers of fibroblasts. The blood vessels in the affected parts often showed proliferated endothelium. In some areas, there were collections of carbon-containing cells suggesting that a lymph node had been completely overgrown, without leaving any other trace of its existence.

The thyroid gland was examined for evidence of the effect of the tumor. The acini of the thyroid gland were irregular in shape and size, although none was large. The colloid material stained poorly. The cells were cuboidal but without papillary infoldings. An occasional area of round cell infiltration was seen, but there was no other suggestion of hyperactivity. Numerous irregular but extensive bands of connective tissue passed in various directions, apparently compromising the form and function of the adjacent acini. In many places, this tissue was infiltrated by a hyaline homogeneous substance, indistinguishable from colloid, suggesting the escape of this material from ruptured acini. At the lower pole, the tumor had begun to infiltrate the gland, displacing the acini and producing the usual degenerative phenomena.

The tumor closely approximated the epithelium of the esophagus, but did not actually touch it at any point. An occasional collection of round cells was seen in the corium.

Invaded and infiltrated portions of the lungs received considerable attention. In that portion of the lung which was invaded by tumor, the tumorous masses had the same appearance as noted previously. There was no special relation between these groups of cells and the exudate lying in the alveoli. Evidence of irritation produced by the growth of the cancer cells was not seen. There were scattered patches indicative of frank bronchopneumonia, and in other portions there was a heterogeneous grouping of cells composed of leukocytes, histiocytes, desquamated alveolar epithelium and an occasional lymphocyte. This heterogeneity was not altered by the occasional presence of masses of fibrin or of serum. The different types of cells were readily distinguishable from each other and from cancer cells, none of them bore the slightest resemblance to amebas. They were not surrounded by any mucoid, homogeneous material. Some of the larger cells were irregularly vacuolated, and a few contained inclusions. The bronchi in these portions contained groups of leukocytes, and either serum, or, in some cases, a little mucoid material. The large mononuclear leukocytes in this exudate had only a superficial resemblance to amebas, such that they might be designated, when in the sputum, as "ameba-like cells."

The general appearance of the tissues in the infiltrated portion of the lower lobe of the right lung was normal. Evidence of bronchopneumonia or cancer cells was not present. The alveoli about the edge of the area were collapsed, and contained practically no free cells. The interstitial tissue contained a few carbon-laden mononuclear leukocytes, and an occasional collection of lymphocytes. Leukocytes were rarely seen. The same description applied also to the infiltrated portion, except that the alveoli were widely dilated and completely filled with a homogeneous material that was colored light pink or bluish, depending on the

intensity of the eosin stain. The adjacent bronchi were filled with the same material (fig 9). The cells lying free in the exudate were widely separated as though a cellular suspension had been highly diluted (fig 10). The alveolar epithelium, in many places, was intact, in others more or less loosened, and the individual cells were somewhat swollen. Those completely detached were slightly larger, and had assumed a circular outline.

There was another type of cell, usually larger and with a slightly larger nucleus. Occasionally, although rarely, the cell contained particles of pigment resembling carbon, but inclusions of various forms were often seen (fig 11). The cytoplasm was foamy, reticulate or vacuolate in structure, the cells which stained a deeper red tended more toward a homogeneous texture. Occasionally two nuclei were seen in a single cell. The shape of the nucleus varied greatly, they were perfectly spherical, elliptic, oval, or of still more irregular form. The chromatin was arranged peripherally, with threads passing radially to meet a centrally placed nucleolus. Tiny bits appeared to be scattered along the threads at irregular intervals. A second nucleolus was occasionally seen. Some of these cells stained less heavily, and the nucleus had a sketchy appearance. The outline



Fig 9—Wall of a bronchus the lumen of which is completely filled with a homogeneous, mucoid, blue-staining material. The irregular masses are condensations of this mucus. Lying free are several cells likely to be mistaken for *Endamebae*, which explains their appearance in the sputum during life. Hematoxylin and eosin  $\times 150$ .

was perfectly preserved but there appeared to be less chromatin present and even this was lighter in tint. In a slide stained with iron hematoxylin the nuclear structure of many of these cells bore a striking resemblance to that of *Endameba histolytica*. With this method of staining, the shape of the nucleus was not altered, but the peripheral distribution of the chromatin was emphasized, as well as the spokelike radiations of the nuclear threads. In those cells with a perfectly round nucleus, the appearance was puzzling. In a few instances, the presence of two chromatin bodies within a nucleus produced a picture that might well be interpreted as a stage in the mitosis of an ameba. The spindles were not clearly distinguishable, but the similarity to chromosomes was close. In one instance the number of these chromosome-like bodies was small, not more than six or eight, thus increasing the similarity. The conclusion reached in regard to these large cells was that they were histiocytes, or mononuclear wandering

cells (also called clasmotocytes), that had been modified in their morphology by reason of their unusual environment. The vacuolation represented an hydropic degeneration in various stages of intensity, and the nuclear changes consisted of a loss of chromatin, but without the appearance of pyknosis or karyorrhexis. It was difficult to be absolutely sure of the complete absence of amebas in this region.

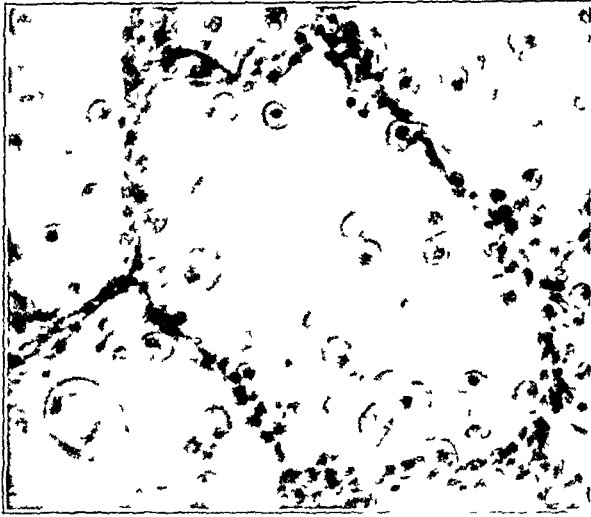


Fig 10—A portion of the lung affected by mucoid infiltration. There is usually little or no change in the alveolar walls, aside from desquamation of more or less of the epithelial lining. Many of these are still attached. Many of the free lying cells resemble *Endamebae*. In the lower left hand corner is an unusually large cell that resembles *Balantidium coli*. (Hematoxylin and eosin,  $\times 150$ .)

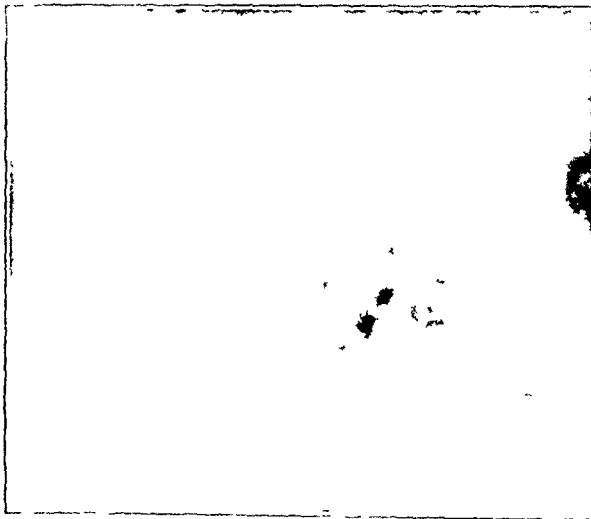


Fig 11—Group of large mononuclear cells, the one in the center of the picture contains the remains of a red corpuscle. Fragments are seen in some of the other cells. (Iron hematoxylin,  $\times 1000$ .)

The pleura and knee joint were examined for evidence of amebic invasion. There was no exudate on the surface of the pleura, and no sign of any amebas passing through this tissue. The vessels were not engorged, and there was no evidence of inflammatory change. The pleura on the right side was no different



from that on the left. Amebas were not recognized in the knee joint. Histiocytes were often seen, especially about the fragments of bone. An occasional area of perivascular accumulation of lymphocytes was found. The synovial membrane was thrown into villi, with slight superficial erosion, and in other portions it was entirely replaced by granulation tissue.

#### COMMENT

The possibility of an infection by *Endameba histolytica* was given serious consideration during the progress of this woman's illness. The idea originated with the observation in the pleuritic fluid of actively motile cells that thrust out pseudopodia and engulfed red corpuscles when they were offered. An occasional nucleus was seen, but vacuoles were not discovered. This activity was preserved on the warm stage, but disappeared when the fluid became cool. Consolidation which was discovered in the lung might have been caused by an abscess, either primary, as has been reported on rare occasions, or secondary to one in the liver. There was a little tenderness over the region of the liver, but there was no jaundice at the time of examination. The patient had lost considerable weight, as do most patients with abscess of the liver. This patient did not have a history of dysentery, although dysentery is not always recorded in these cases. Constipation occasionally accompanies amebic infections, especially those of the extremely chronic type. In New Mexico, where the patient had lived, there is a rather high incidence of amebic infections, and in fact such infections are being recognized with increasing frequency in various parts of the United States. An appreciable percentage of hepatic abscesses occurs without history or sign, clinically or pathologically, of ulceration of the bowel.

The laboratory reported the presence of ameba-like cells in the sputum, and later, in the urine, but none could be found in the feces. It was then recalled that frequent reports are found in the current literature of amebic bronchitis, amebic bronchopneumonia, amebic cystitis and amebic nephritis, in fact, of various extra-intestinal nonsuppurative visceral localizations of *Endameba histolytica*. These had not been reported from this country as yet, but if they occurred in certain countries, there was no reason why they should not be found in the United States.

The roentgenographic report of a peculiar form of periostitis recalled the report of a type of arthritis, especially of the hip, in which amebas had been reported. If amebic arthritis of the hip were known to exist, it might be more extensive and might involve other joints as well.

Emetine has been credited with a cure in all the nonsuppurative cases of amebic infection of the lung, bronchi, urinary bladder, and kidneys, and with having exerted beneficial action in various more obscure lesions supposed to be related to this form of infestation. Emetine was tried, therefore, with what seemed to be phenomenal suc-

cess After a short time, however, the improvement seemed to stop, and the patient began to lose strength. Difficulty in swallowing developed, and observers again entertained the idea of a malignant condition. Later a malignant condition was proved to exist, but the idea persisted that there might still be an amebic infection present.

Even at the time of necropsy, several characteristics were noted that had a bearing on possible amebic infection. There was a mass of adhesions between the diaphragm and the liver, as though a previous infection might have passed from the liver through the diaphragm, but scars were not present to indicate a definite abscess of the liver or area of diffuse hepatitis. The intestine did not reveal evidence of present or past amebic infection. The portion of the lung nearest to the right pleura was consolidated, and from the cut surface could be squeezed brownish mucus identical in color and consistence with that so often seen in the stools from patients with amebic colitis. The cause of this consolidation could not be attributed to obstruction of the connecting bronchus by the developing carcinoma, for the bronchus seemed to be clear. Microscopically, the cells in this area were different from those found in any other portion of the body, and radically different from those in other parts of the lung. These cells were neither cancer cells, nor epithelial cells cast off by desquamation. Some of them reproduced accurately the various forms of amebas observed in other lesions. However, the wide variations in the appearance of the nuclei in cells otherwise apparently identical was the deciding factor against their being amebas. Still, the thought remained that among these cells there might have been a few amebas which had been capable of prolonging the diseased condition of the lung even though they might have been mingled with abnormal cells of the human body. The decision on the last point has been the most difficult of all, but it is felt that the existence of amebas could not be demonstrated. On this new basis, the clinical data may be reviewed without reference to the possibility of amebic infection, but with the carcinoma of the lung and other lesions considered as predominant.

Chronic bronchitis doubtless had been present for years, with later development of the bronchogenic carcinoma. Pain in the right upper quadrant was caused by gallstones and involvement of the right kidney. Associated with the disease of the gallbladder was mild hepatitis which left a few adhesions between the capsule and the diaphragm. The focal necrosis must have been of recent origin, possibly attributable to sepsis from the infection of the kidney. The pleurisy of the right side might have been an irritative phenomenon from the development of a cancerous nodule beneath the pleura, and the consolidation of the dependent portion of the affected lung might have been attributed to immobilization and lack of proper conditions for the removal of

exudate by the bronchial epithelium. The periosteal lesions were probably on the basis of focal infection from the condition of the lung and thus corresponded rather remotely to the so-called pulmonary osteo-arthritis. The apparent beneficial effect of emetine was not caused by the removal of an amebic infection, but was attributable to a systemic effect which the use of this drug is known to produce in various forms of pulmonary disease.

Without a thorough study of this case it is felt that the conditions present might have led to a report of nonsuppurative, amebic bronchopneumonia, complicated by a carcinoma of the lung. It is felt that most of the current reports of amebic infections of the lungs, and so forth, are based on even less evidence than is here presented, and that the conclusions are erroneous for the reasons that can be deduced from this detailed account. It is not sufficiently appreciated that body cells under proper conditions can be extremely active, and that their morphology can be easily confused with that of amebas. Furthermore, cells that look, and perhaps act, like amebas, in the sputum and urine, may not be amebas. The improvement under treatment with emetine is not a diagnostic point in favor of an amebic infection as is so commonly supposed.

#### SUMMARY

A detailed case report is presented in which there was reason to suspect an infection with *Endameba histolytica*, but which proved to be a bronchogenic carcinoma associated with hydrothorax, mucoid infiltration of the lung and disease of the gallbladder and kidney.

Certain cells, when observed on the warm stage, manifested activity and assumed morphology that might readily lead to confusion with amebas.

Cells of the human body, especially histiocytes, under pathologic conditions simulated amebas when viewed in sections stained either with hematoxylin and eosin or with iron hematoxylin.

One case does not justify sweeping conclusions, but the intensive study of this case involved extensive search of the literature and was made against a background of many years of work in parasitology. Therefore, it is safe to conclude that if there is doubt as to a given cell in the body being an ameba, it probably is not. Disregard of this as a criterion may lead to further erroneous conclusions.

# THE IDENTITY OF SO-CALLED AGRANULOCYTIC ANGINA

REPORT OF A CASE<sup>1</sup>

EDWARD ROSE, M D

AND

KARL MUSSER HOUSER, M D

PHILADELPHIA

Agranulocytosis or agranulocytic angina, so called, was described as a clinical entity by Schultz<sup>1</sup> in 1922. Since that time it has been widely accepted as such, numerous additional cases have been reported, and the name has come to be regarded by many clinicians as descriptive of a hitherto undescribed disease entity. A number of writers have maintained, however, that the picture described by Schultz was not specific, with this view we agree. In addition to recording an additional case showing necrotic oropharyngeal lesions, agranulocytic leukopenia and general sepsis, we wish to review briefly the clinical and pathologic features of the cases previously reported and to consider several possible explanations for the picture produced. The view that so-called agranulocytosis simply constitutes a type of leukopenic reaction to an overwhelming infection seems to us to be nearest the truth, and the one on which we wish to place greatest emphasis.

Schultz reported six patients, all middle-aged women, who showed gangrenous stomatitis and pharyngeal lesions associated with fever. There was a marked reduction in the number of circulating leukocytes with a relative increase in lymphocytes to as high as 100 per cent, polymorphonuclear leukocytes being markedly decreased in number or absent. The picture was one of profound sepsis, and, in all cases, death occurred in a few days. The name, agranulocytic angina or agranulocytosis, was given to the condition. Leon<sup>2</sup> attempted to classify it as a clinical entity soon after Schultz' description appeared.

Although, as Hirsch<sup>3</sup> pointed out, similar cases had been described by Schwarz<sup>4</sup> in 1904, by Turk<sup>5</sup> in 1907, and by Marchand<sup>6</sup> in 1913,

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<sup>1</sup> Submitted for publication, Oct. 22, 1928.

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1 Schultz, W. Different Throat Infections, *Deutsche med. Wchnschr.* **48** 1495, 1922.

2 Leon, A. Agranulocytosis, *Deutsches Arch. f. klin. Med.* **143** 118, 1923.

3 Hirsch. Agranulocytic Angina, *Munchen med. Wchnschr.* **74** 762, 1927.

4 Schwarz, L. A Case of Extreme Leukopenia, *Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. in Wien* **3** 190, 1904.

5 Turk, W. Septic Diseases with Destruction of Granulocytes, *Wien. klin. Wchnschr.* **20** 157, 1907.

6 Marchand. Unusual Lymphocytosis in Early Infection, *Deutsches Arch. f. klin. Med.* **110** 359, 1913.

Schultz report stimulated a number of descriptions of similar cases. A survey of the literature up to the present shows a total of seventy-eight reported cases which fall within the group termed agranulocytic angina.

Kastlin,<sup>7</sup> in 1927, analyzed forty-three reported cases of so-called agranulocytic angina and added descriptions of two more. Gundrum,<sup>8</sup> in 1928, added another instance and noted three others reported after Kastlin's review was published, thus bringing the total number of cases to forty-nine. A search of the literature revealed the following twenty-eight cases not mentioned by Kastlin or Gundrum, which, with the present instance, brings the total number described to seventy-eight. Hart,<sup>9</sup> 1 case, Flandin,<sup>10</sup> 1 case, Schaefer,<sup>11</sup> 4 cases, Hill,<sup>12</sup> 1 case, Licht and Hartmann,<sup>13</sup> 1 case, Cannon,<sup>14</sup> 1 case, Prendergast,<sup>15</sup> 1 case, Chiari,<sup>16</sup> 1 case, Dahlen and Wahlgren,<sup>17</sup> 1 case, Zikovsky,<sup>18</sup> 2 cases, Bruggeman,<sup>19</sup> 3 cases, Baltzer,<sup>20</sup> 3 cases, Borchers,<sup>21</sup> 1 case, Hirsch,<sup>22</sup> 6 cases, and Koehler,<sup>23</sup> 1 case. One of Cannon's cases is not included because of inadequate description. In Prendergast's case, the patient had a total leukocyte count of 10,000, but granular cells were not present, and at autopsy there was an almost complete absence of granulocytes.

7 Kastlin, G. J. Agranulocytic Angina, *Am J M Sc* **173** 799 (June) 1927

8 Gundrum, L. K. Agranulocytic Angina. Report of a Case, *Arch Int Med* **41** 343 (March) 1928

9 Hart, V. K. A personal communication

10 Flandin, M. A Case of Agranulocytosis, *Bull et mem Soc med d hop de Paris* **50** 1459 (Oct.) 1926

11 Schaefer, R. Differential Diagnosis of Agranulocytosis, *Deutsches Arch f klin Med* **151** 191, 1926

12 Hill, H. P. Acute Leukemia and Agranulocytic Angina, *California & West Med* **25** 609 (Nov.) 1926

13 Licht, H., and Hartmann, E. Agranulocytosis, *Deutsche med Wchnschr* **51** 1518 (Sept.) 1925

14 Cannon, A. B. Unusual Dermatoses, *South M J* **20** 141 (Feb.) 1927

15 Prendergast, D. A. A Case of Agranulocytic Angina, *Canad M A J* **17** 446 (April) 1927

16 Chiari, Hank, and Redlich, F. The Question of Agranulocytosis, *Wien klin Wchnschr* **39** 1510 (Dec.) 1926

17 Dahlen, B. and Wahlgren, F. Contribution to the Knowledge of Agranulocytosis, *Acta med Scandinav* **65** 407, 1926-1927

18 Zikovsky, A. Agranulocytosis, *Wien med Wchnschr* **77** 589, 1927

19 Bruggeman, K. Agranulocytosis, *Ztschr f Hals-, Nasen- u Ohrenh* **15** 187 1927

20 Baltzer, H. Agranulocytosis, *Arch f path Anat* **262** 681, 1926

21 Borchers, K. A Case of Agranulocytic Angina, *Ztschr f Laryngol, Rhinol* **15** 386 (April) 1927

22 Hirsch, C. Angina Agranulocytotica, *Munchen med Wchnschr* **74** 762, 1927

23 Koehler, G. Aleukemia and Agranulocytosis, *Deutsches Arch f klin Med* **155** 155, 1927

from the marrow of the sternal end of the clavicle, it is therefore included in this series

Despite considerable clinical and pathologic variation in particulars, there are features in the reported cases which are sufficiently striking and frequent to warrant description. The majority of patients have been women, usually in middle age. The onset is usually acute, but sometimes occurs after previous illness. Fever is early and constant, and profound prostration is common. Jaundice was present in 58 per cent of the cases collected by Kastlin. Other prominent symptoms are sore throat, malaise, chills and dysphagia. The course of the disease is usually acute, death occurring in the great majority of cases in from four to eight days, although a few patients have survived for from four to six weeks. Necrotic or ulcerative processes have been observed almost constantly in various parts of the oral cavity, occasionally lower in the gastro-intestinal tract (the esophagus, stomach, duodenum, ileum, colon, anus and rectum), in the cervix and vagina or on the cutaneous surfaces. Cutaneous and visceral hemorrhages have been encountered. In most of the recorded instances, the blood platelets have been normal in number. The spleen and liver have occasionally been found to be enlarged. At autopsy lymphoid collections have been observed in both organs, and endotheliosis in the spleen.

A variety of organisms have been recovered from the oral lesions, including Klebs-Löffler bacilli, Vincent's spirochetes and fusiform bacilli, pneumococci, *Bacillus pyocyaneus* and streptococci of various types. Hemolytic streptococci, staphylococci, *B. pyocyaneus*, *B. coli*, pneumococci and *Streptococcus viridans* (Cannon<sup>24</sup>) have been recovered from the blood, although in the great majority of instances cultures of the blood remained sterile.

The pathologic observations may be summarized as follows from the analysis of the autopsies reported:

- 1 The lungs in many instances have shown fibrinous confluent bronchopneumonia, with little if any evidence of inflammatory cellular reaction. Pleurisy with effusion and subpleural petechiae have been noted a few times.

- 2 The liver has sometimes been found to be enlarged, often with perivascular lymphocytic collections. Focal and bacterial emboli have been noted.

- 3 The spleen is frequently noted as enlarged ("acute splenic tumor"). Bacilli and inflammatory exudate are found in and beneath the capsule. Marked proliferation of endothelial cells, with little if any increase in lymphocytes has been a common feature.

- 4 In the lymph nodes, small hemorrhages, and, occasionally, hyperplasia of endothelial cells, have been observed.

- 5 The heart has shown parenchymatous degeneration, subepicardial and endocardial hemorrhages, and, in one of Kastlin's cases, acute verrucous endocarditis.

- 6 The kidneys are mentioned (Piette<sup>24</sup>) as showing numerous bacterial emboli which were present also in the suprarenal bodies.

<sup>24</sup> Piette, E. C. The Histopathology of Agranulocytic Angina, J. A. M. A. 84: 1415 (May 9) 1925.

7 In the stomach and intestines there may be superficial necrotic foci with a surrounding zone of lymphocytes, bacterial emboli and petechial hemorrhages in the mucosa

8 The tonsils and pharynx have almost constantly shown ulcerative or gangrenous lesions of greater or less degree. These are often surrounded by an edematous zone and sometimes by a profusion of bacterial collections

9 The bone marrow is often described as "red," as in twenty-seven of thirty-three autopsies mentioned by Kastlin. When it is fatty, little or no decrease in granular cells is found. In these cases, the histologic structure has been found to be poor in cells, with granular cells greatly decreased or completely absent. The lymphocytes are often prominent by contrast. Reticulo-endothelial cells are increased. In general, the erythrocytes are little affected, and their germinal centers appear normal, but in a few instances an excess of nucleated red cells has been observed.

10 In the case here reported there were curious widespread patches of necrosis involving the walls of the smaller arteries and veins with hyalinization of their contents, this was particularly noticeable in the areas of subcutaneous necrosis. Diffuse patches of necrosis without evidence of cellular reaction were noted as occurring in various organs such as the lung, spleen and liver, as well as in the bone marrow.

The blood picture is striking. In practically all instances, there is a marked absolute reduction in leukocytes, the lowest count recorded being 100 per cubic millimeter. Polymorphonuclear leukocytes either are entirely absent or constitute less than 6 per cent of the white cells. In one instance, however, 22 per cent of polymorphonuclears are noted. The lymphocytes are always relatively increased, sometimes up to 100 per cent. In the case reported by Piendeigast, the leukocyte count was 10,000 per cubic millimeter, with 90 per cent small, and 10 per cent large, lymphocytes. Endothelial cells, premature lymphoid forms, and occasionally eosinophils—in one case 12 per cent—are seen in the blood smears. The lymphocyte, however, is the predominating white cell.

Naturally, a number of views have been advanced as to the etiology and nature of this process. The principal opinions may be summarized as follows:

1 The condition constitutes a specific disease entity (Roch and Mozer,<sup>25</sup> Schultz and Jacobowitz,<sup>26</sup> Baltzer,<sup>27</sup> Hunter,<sup>27</sup> Gundrum<sup>8</sup> and Hirsch<sup>28</sup>), there is also primary disease of the granuloleukopoietic apparatus and secondary necrotic foci (Bantz,<sup>8</sup> and Lovett<sup>29</sup> and Rosler<sup>30</sup>)

25 Roch, M., and Mozer, J. Angina Agranulocytotica, *Presse med* **34** 1171 (Sept.) 1926

26 Schultz and Jacobowitz. Agranulocytosis, *Med Klin* **21** 1642 (Oct.) 1925

27 Hunter, R. J. Agranulocytic Angina. Report of a Case with Fracture of the Tibia, *Laryngoscope* **38** 348 (May) 1926

28 Bantz, R. The Question of "Agranulocytosis," *Munchen med Wchnschr* **72** 1200 (July) 1925

29 Lovett, B. R. Agranulocytic Angina, *J. A. M. A* **83** 1498 (Nov. 8) 1924

30 Rosler, O. Unusual Diseases of the Blood, *Wien med Wchnschr* **77** 63, 1927

2 The progenitors of the granular cells (or the bone marrow) are injured by a specific noxa, the organism then being rendered defenseless against secondarily invading bacilli which produce the visceral and oral lesions (Licht and Hartmann,<sup>33</sup> Skiles<sup>31</sup> and Kastlin<sup>7</sup>)

3 The condition is the result of infection superimposed on a pre-existing hypoplasia of the granulocytogenic apparatus (Dahlen and Wahlgren<sup>37</sup>)

4 It is a form of "malignant leukopenia" to be grouped with septic or leukemic conditions showing a reduced percentage of neutrophils (Pelnar<sup>32</sup>)

5 The ulcerative lesions are produced by bacterial emboli following a primary attack on the granulocytogenic centers, leaving only the reticulo-endothelial elements to offer resistance (Piette<sup>4</sup>)

6 The condition is a type of reaction to an overwhelming septicemia in a subject with low resistance (Jaffe,<sup>33</sup> Koehler,<sup>33</sup> Hart,<sup>9</sup> Weiss,<sup>34</sup> Mouzon,<sup>35</sup> Rotter,<sup>36</sup> Zadek,<sup>3</sup>), or a terminal reaction in other conditions, as Hodgkin's disease (Jaffe<sup>33</sup>)

The case which was observed by us in 1927 and reported in this article conforms in its clinical and pathologic features with the majority of the reported instances of so-called agranulocytic angina

#### REPORT OF CASE

*History*—Mrs M F, aged 48, who was first seen on the night of Jan 26, 1927, complained of malaise, sore throat, chills and fever, of one day's duration. She gave a history of frequent attacks of quinsy during most of her life. These were not confined exclusively to either side of the throat. She estimated their frequency at once or twice a year. Incision had often been necessary, but sometimes the abscesses had evacuated spontaneously. She had never had a tonsillectomy. For nine years she had been free from sore throat. Occasionally she had arthritic pains in the ankles after such attacks but never rheumatic fever, chorea or any cardiac disturbances. She had been operated on for removal of a fibroid tumor of the uterus five years before. Her previous history was otherwise negative. The family and social histories were negative.

*Examination*—When first seen, the patient appeared acutely ill, with a hot flushed skin and a temperature of 103 F. The pulse was rapid. Examination of the heart and lungs showed nothing of significance. The left peritonsillar area showed distinct bulging. There was an indurated swollen area just below the middle of the left maxilla, with dusky discoloration and moderate tenderness. The liver and spleen were not palpable. Petechiae or other skin eruptions were not present. A small myringotomy knife was introduced into the soft palate above the left tonsil. Bleeding was free but pus was not obtained. On the following day, the general condition was about the same except that the swelling was more marked.

31 Skiles, J H. Agranulocytic Angina, *J A M A* **84** 364 (Jan 31) 1925

32 Pelnar. Malignant Leukopenia, *Čas lek česk* **63** 1653, 1924

33 Jaffe. Hodgkin's Disease and the Agranulocytic Symptom Complex, *Munchen med Wchnschr* **73** 2012, 1926

34 Weiss, U. Lymphatic Reaction and Agranulocytosis with Lethal Sepsis, *Ztschr f klin Med* **106** 617, 1927

35 Mouzon, J. Agranulocytosis, *Presse mcd* **34** 1269 (Oct) 1926

36 Rotter, W. Pathological Anatomy of Agranulocytic Disease, *Arch f path Anat* **17** 258, 1925

37 Zadek. Agranulocytosis, *Med Klin* **21** 685 (May) 1925



Another incision did not yield pus, and the subsequent introduction of a small hemostat was without result

On January 31, the patient was admitted to the Hospital of the University of Pennsylvania. At that time, she was having frequent chills and was slightly irrational. The pulse rate ranged from 96 to 130 and the temperature from 101 to 104 F. Examination of the blood showed 600 leukocytes with lymphocytes 100 per cent and hemoglobin 82 per cent. At the time of admission, there was marked swelling of the left half of the soft palate with a distinct soft elevation posterior to the last molar tooth. A slough, about 2 cm in diameter, occupied the center of the swollen area with a sinus about 1 cm in depth at its lateral inferior aspect. A smear from the throat showed a large number of Vincent's organisms, a few micrococci and diplococci, but no Klebs-Loeffler bacilli. The patient was seen in consultation by Dr O H P Pepper, who advised the intravenous administration of neoarsphenamine, including local applications to the throat, and blood transfusion.

*Treatment and Course*—After the administration of 0.3 Gm of neoarsphenamine intravenously, the patient vomited and the temperature rose to 104 F. On the following day the swelling and induration in the neck were less marked. There were a number of erythematous blotches over the entire body which increased rapidly in size during the day and in the afternoon showed punctate suppurative areas in their centers. Five hundred cubic centimeters of citrated blood was administered followed by a second injection of 0.3 Gm of neoarsphenamine. A blood culture taken on admission showed an abundant growth of type III pneumococcus. Organisms which were similar morphologically were seen in smears made from the skin lesions.

The abundant recovery of organisms of this sort from the blood stream would seem of great importance in indicating that a general pneumococcic septicemia was the major factor operative in producing the clinical picture, including the granulocytic leukopenia. The occurrence of other organisms in the blood stream in other cases is, of course, of equal significance. It is unfortunate that the chronological relationship between the invasion of the throat by the Vincent's organisms and of the blood stream by the pneumococci cannot be established.

The leukocyte count on February 1 showed 500 per cubic millimeter with 100 per cent lymphocytes. The abdomen remained slightly distended. The spleen and liver were not palpable. Pneumococcus antibody solution was given in 25 cc quantities at intervals of six hours. The condition of the patient rapidly became worse. Death occurred on February 2.

*Autopsy*—Autopsy was performed four hours after death by Dr Benjamin Gouley. The following observations were reported after histologic study by Dr Baldwin Lucke.

There was a generalized skin eruption of small subcutaneous nodules, the size of a pea. The liver was slightly enlarged. An acute necrotizing inflammation of the tonsils and peritonsillar tissues was found, especially on the left side, with gangrene of the left tonsil and adjacent tissue. Edema and inflammation of the laryngeal mucosa appeared with several small ulcerations in the larynx itself and on the edge of the epiglottis. The spleen was enlarged and soft, while the swollen liver contained numerous white structures about the size of miliary tubercles, there was cloudy swelling and fatty degeneration. Gross examination of the heart, lungs and kidneys showed nothing of interest.

Microscopic examination revealed marked necrotic changes in the walls of the subcutaneous arterioles and veins in the areas of the nodular eruption, these vessels containing a hyaline or coarsely granular material. There was necrosis around the pharyngeal and laryngeal ulcerations, with a conspicuous scarcity of

exudative cells and no leukocytes in the vicinity. The edges of the tonsillar ulcer was structureless and contained large masses of bacteria. In the lung a number of patches were present, where the alveoli were flooded with partly fused erythrocytes or blocked by a net of fibrin. Exudative cells were generally absent. The alveolar walls and the walls of the arterioles and venules of these patches were usually frankly necrotic. In the spleen the sinusoids and pulp cords were packed with erythrocytes, the monocytes appearing inconspicuous. A few arterioles showed frank necrosis. A number of necrotic areas were found in the liver, without any evidence of cellular reaction.

The bone marrow, in the middle of the femur, showed replacement of fat by hyperplastic marrow. There was marked scarcity of myeloid cells, and many of

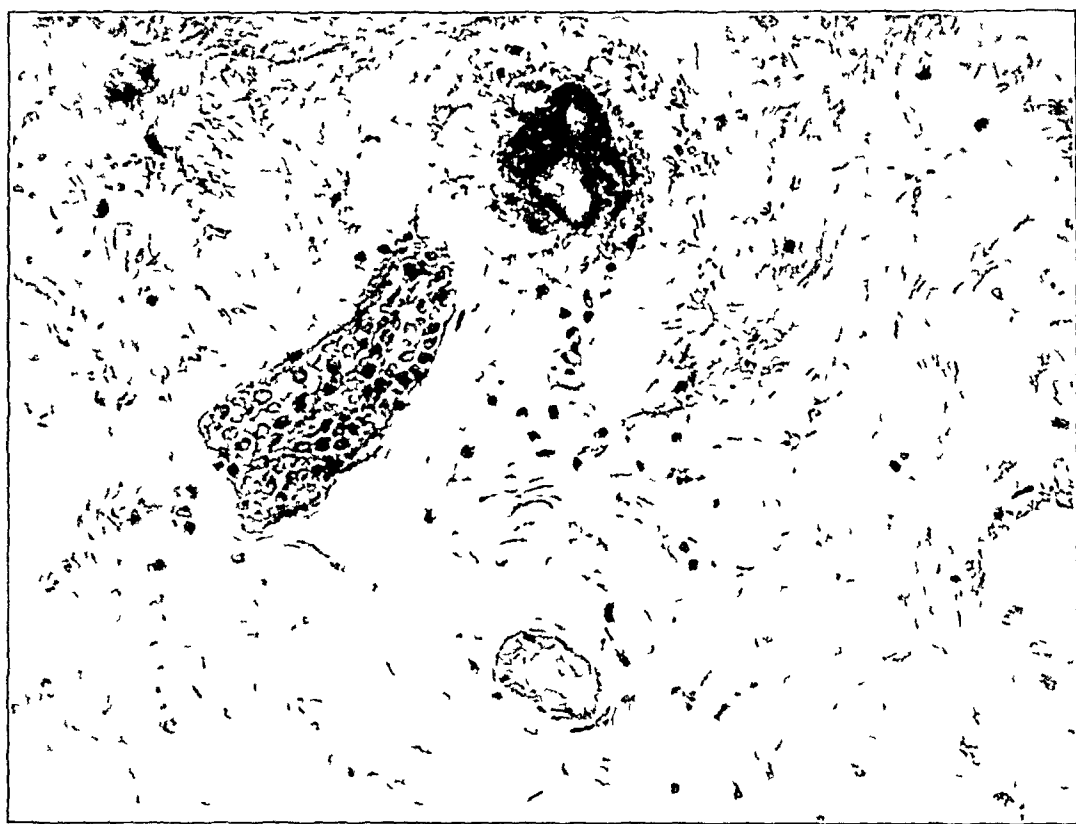


Fig 1—Subcutaneous tissue, showing marked edema and a few lymphocytes and plasma cells. No leukocytes are present. The walls of the arterioles are structureless or necrotic.

these showed degeneration. No leukocytes of any kind were found. Necrotic changes of vessels were not found, although a few completely necrotic patches were present. The most striking and significant observations were (1) the widespread necrosis of arterioles and venules, (2) the complete absence of leukocytes, even in the bone marrow, (3) the diffuse occurrence of small patches of necrosis without cellular reactions, (4) necrotic areas in the pharynx, larynx and tongue, and (5) areas of inflammatory edema, especially in the upper respiratory tract and skin.

*Detailed Pathologic Report*—There was a prominent skin eruption over almost the entire body, especially on the face, neck, arms and upper part of the trunk. It consisted of small subcutaneous nodules, from pink to light red and about the size of a pea. Neither edema nor jaundice was observed.

The bladder was somewhat distended, and the liver was moderately enlarged. Lymphadenopathy of the left cervical glands was found. There was an acute necrotizing inflammation of the tonsils and of the peritonsillar tissues, especially on the left side, consisting of gangrene of the left tonsil and adjacent tissue without distinct formation of pus. The right side did not show the same extreme destruction. The tissues of the upper part of the neck were generally edematous with distinct enlargement of the small lymphatic collections throughout the fatty areolae. The upper edge of the epiglottis showed two or three superficial ulcerations, grayish-yellow patches that had not broken down. Extreme edema of the epiglottis and the neighboring tissues almost closed the orifice. The larynx had a reddened, swollen mucosa which showed several small superficial ulcers.

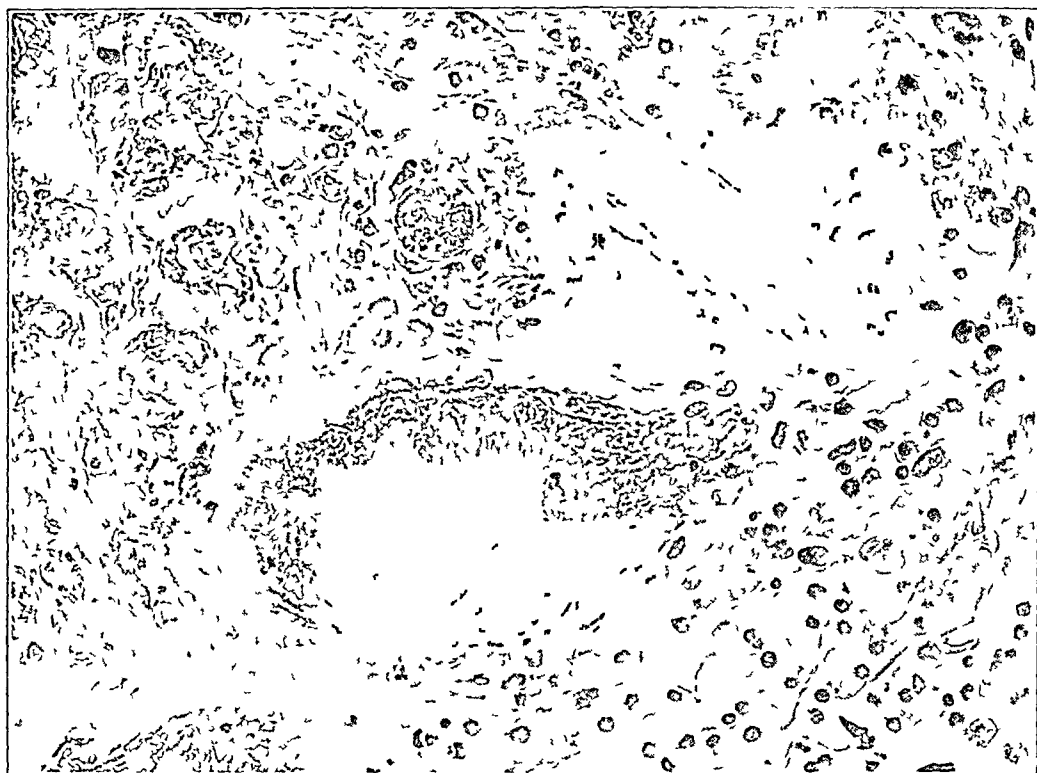


Fig 2—Peritonsillar tissue, showing a necrotic area. No leukocytes are present.

Nothing of note was found in the heart.

In the left lung, there was marked emphysema, with a mild congestion of the bronchial mucosa. Generalized emphysema and moderate congestion were observed in the right lung.

The spleen was enlarged and rather soft. Follicles and fibrous markings were not visible.

In the left kidney, generalized hyperemic streaking was seen through the cortical tissue.

The liver was enlarged and pale brown with a smooth edge. Through the capsule were many small, white structures about the size of miliary tubercles. On section, the tissue of the liver showed cloudy swelling, and early fatty degeneration. The small white nodules were apparently of the same structure as the cutaneous nodules.

The periaortic and iliac lymph nodes showed the same type of hypertrophy as seen in the cervical groups of nodes

The right femur and tibia were opened. Bone marrow from the midpart of the femur showed a distinct dark red hyperplastic change. Marrow from the tibia, on the other hand, was yellowish, fatty, edematous and did not show hyperplasia.

*Microscopic Examination*—Section was made through the nodular eruption. The epidermal cells were swollen, and contained poorly defined vacuoles best seen around the nuclei. The fibers of the corium were widely separated, and many were fractured. The widened interspaces contained finely granular eosin-staining precipitate and a delicate fibrin net. All the vessels were engorged, the erythrocytes being partly fused. There were several small hemorrhages. The walls of most

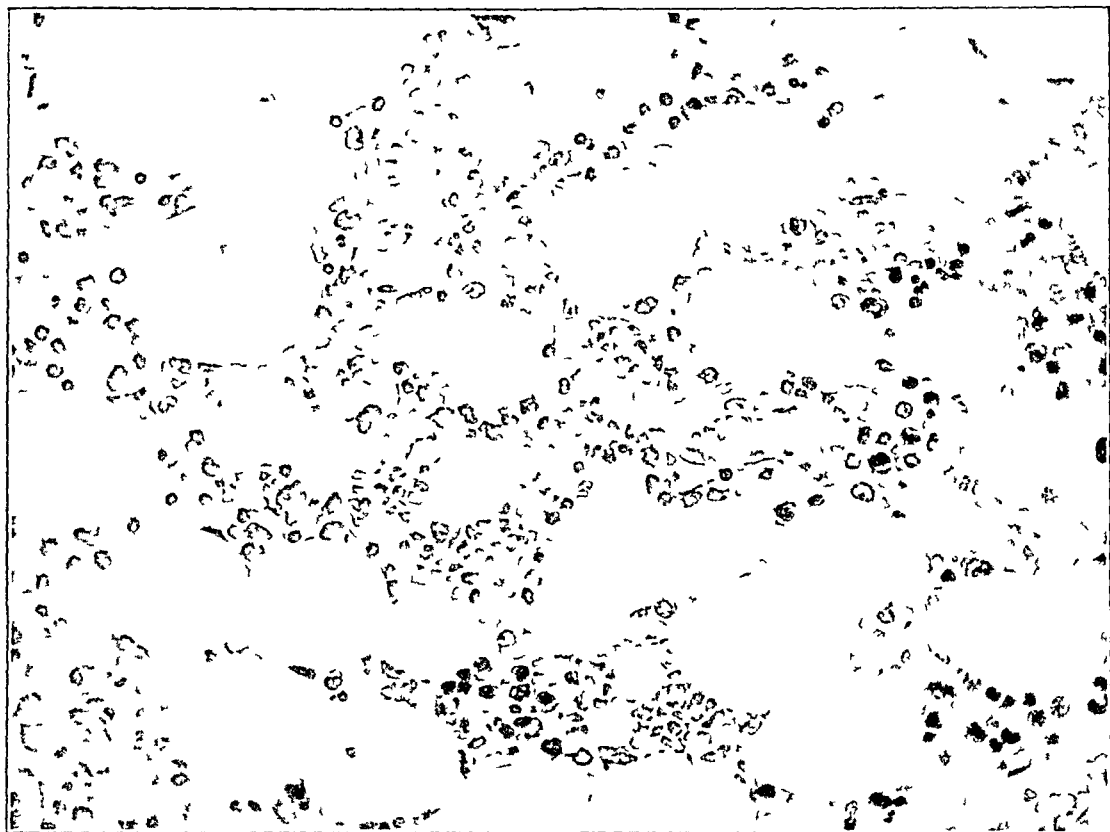


Fig. 3—Bone marrow, showing engorgement of capillaries and great scarcity of myeloid cells

of the arteries and veins had a hyaline or lumpy appearance, details of structure having disappeared completely. These necrotic vessels generally contained a hyaline or coarsely granular material. The perivascular tissue was particularly loose, and contained fibrin nets. Occasional small groups of plasma cells, lymphocytes and monocytes were encountered, but leukocytes were absent. In the deeper portions of the corium, the collagenous fibers were considerably swollen. The sweat and sebaceous glands were practically normal.

A section of the larynx was taken from an ulcerated area. At some distance from the ulcer the cells of the mucosa were normal, the cilia were well preserved. Near the edges of the ulcer the mucosal cells were vacuolated, the cilia were lost and various nuclear degenerative changes existed. At the edge of the ulcer the cells were frankly necrotic. The ulcer measured about 7 mm in length.

The mucosa was completely absent. The basement membrane still persisted as an irregularly thickened hyaline band. The subjacent membrana propria was extremely edematous. The component elastic and collagenous fibrils were largely broken. Their remnants appeared as eosin-staining, coarse granules or short rods enmeshed by delicate fibrin nets. There was a conspicuous absence of exudative cells, only in the deeper portions, adjoining the mucous glands, were found occasional minute collections of plasma cells and lymphocytes and rarely a large clasmatocyte. Leukocytes were not present. The capillaries were inconspicuous. About one half of the arterioles and venules were frankly necrotic. The mucous glands showed various degenerative changes ranging from cellular swelling, through excessive granularity and vacuolization, to frank necrosis. The cartilage and the peritracheal areolar tissues were normal.

Section was made through an ulcerated area on the posterior portion of the tongue. The surface epithelium was completely destroyed. All of the tissue

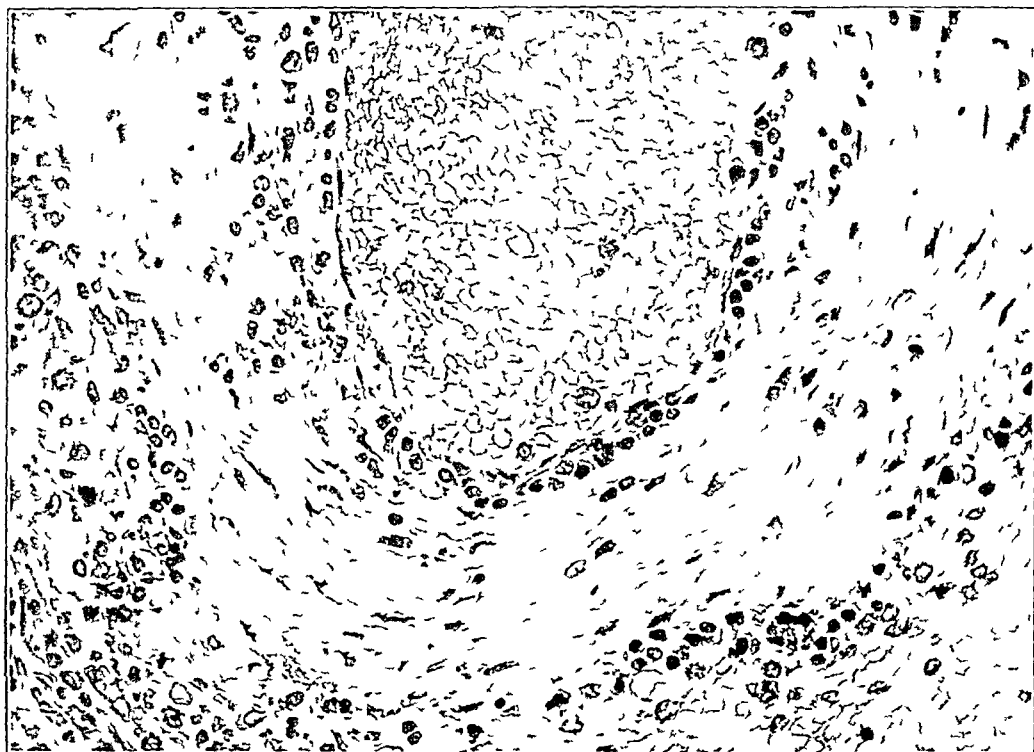


Fig 4—Spleen, showing necrosis of the wall of an artery, with subintimal infiltration

lying beneath the eroded surface was necrotic, and consisted of barely recognizable fragmented muscle cells and connective tissue fibers. The structureless mass had a loose texture. It was permeated by a broken, rather granular mass of fibrin in which were embedded degenerated plasma cells and lymphocytes. In a few patches there were fairly well preserved but loosely arranged collections of lymphoid tissue. The various glands of the deeper portions of the tongue were partly or completely necrotic. The vessels had necrotic walls. The tissue adjoining the necrotic area was moderately edematous, but otherwise unchanged. As in the sections already described, there was a conspicuous absence of leukocytes.

Examination of the right tonsil and peritonsillar tissues (including several lymph nodes) revealed that large areas of the tonsil and the peritonsillar tissue had been

completely destroyed. The edges of the ulcers were completely structureless, and consisted of a granular eosin-staining mass in which lay large colonies of bacteria. The non-necrotic portions of the tonsil and peritonsillar tissues were extremely edematous, and permeated with fibrin which in many places appeared in the granular nonfibrillar form. The lymph sinuses contained great numbers of branching polyhedral reticular cells. Similar elements occurred in the loose edematous peritonsillar tissues. There were, in addition, moderate numbers of plasma cells, and in the adenoid tissue, occasional mononuclear giant cells. Leukocytes were not found. Many vessels had necrotic walls. Several groups of muscle fibers either were swollen or hyalinized, or had lumpy, vacuolated, broken-up cytoplasm. Between such degenerating muscle cells were found considerable numbers of monocytes, plasma cells and lymphocytes, many of these infiltrating cells had undergone degeneration.

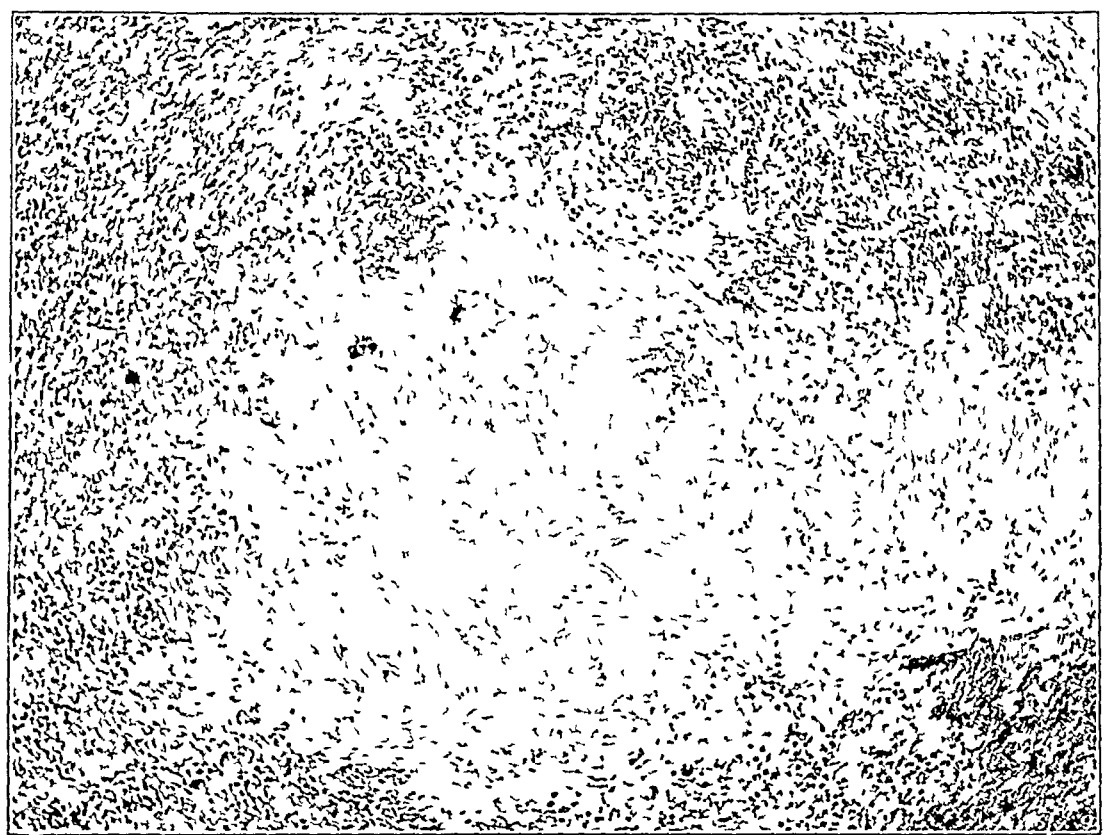


Fig. 5—Spleen showing a necrotic patch and disappearance of cells (low power)

In the lung there were a number of small patches, measuring from less than 1 mm to several millimeters in diameter, in which the air spaces were flooded with partly fused erythrocytes, or blocked by a dense fibrin net. Exudative cells were generally absent, but occasional large mononuclear elements were encountered. The alveolar walls and the walls of the arterioles and venules of these consolidated patches were usually frankly necrotic.

Microscopic examination of tissue from the heart did not show any significant changes.

The capsule and trabeculae of the spleen were normal. The structural details of the pulp were difficult to distinguish because the sinusoids and pulp cords were packed with erythrocytes. The endothelial lining of the sinusoids was not swollen.

There were no foreign cells with the sinusoids or the pulp. The extreme engorgement so overshadowed the general picture that the splenic monocytes appeared as inconspicuous collections. The follicles were of average size, and composed of the usual elements. Most of the arteries had normal walls, but a few showed the frank necrosis described in other organs. Several patches of splenic tissue, each about 1 mm. in size, were completely structureless, and appeared as pale eosin-staining areas through which were scattered hyaline lumps. The framework was only partly preserved, since it, too, had undergone necrosis. There were no cells in these areas.

The cells of the liver in general were somewhat swollen, but normally nucleated. Most of them contained an abundance of minute droplets of fat. In almost every low power microscopic field one or two greatly swollen, deep eosin-staining, non-nucleated, hyalinized liver cells were found. The sinusoids were poorly filled and did not contain foreign cells. There were several patches of pale-staining necrotic areas, about 1 mm. in diameter. The framework was still preserved, but the cells of the liver had largely disappeared. A few hyaline lumps were probably necrotic cells not yet autolyzed. There was no cellular reaction.

Microscopic examination of tissue from the kidney showed nothing significant.

In the bone marrow from the middle of the shaft of femur, about two thirds of the fat had been replaced by hyperplastic marrow. The capillaries were moderately engorged. The cellular groups and islands were arranged rather loosely and consisted chiefly of erythrocytes, erythroblasts and macroblasts. There was an astonishing scarcity of myeloid cells. Many of those present showed distinct degeneration, their outline was indistinct and ragged, the cytoplasm tended to take an eosin-stain, or it contained hyaline droplets. Degenerated cells of this kind usually have a pale ballooned, or small pyknotic, nucleus. Entire cells were transformed into a hyaline mass. No leukocytes of any kind were found. There was an average number of megalokarocytes, but many of them showed cytoplasmic and nuclear changes similar to those of the myelocytes. In brief, there was an active erythrocytic regeneration and a myelocytic destruction. Changes in the vessels like those described for other sections, were not found here. There were, however, a number of small patches in which the entire tissue was completely necrotic, the general appearance being similar to the necrotic areas in the spleen and liver.

*Resume*—The lesions common to the various organs were small patches of necrosis without cellular reactions. There was widespread necrosis of the walls of smaller arteries and veins, and a complete absence of leukocytes, even in the bone marrow. Areas of inflammatory edema were found, especially in the upper respiratory tract and skin.

#### OBJECTIONS TO THE CONCEPTION OF AGRANULOCYTOSIS AS A DISEASE ENTITY

While the hypothesis which assumes the condition to be a specific disease entity is in some respects attractive, certain objections to its acceptance arise, the more important of which are as follows:

1. Marked leukopenia, with decrease or disappearance of neutrophils, is well known to occur occasionally in severe infections of different types, namely, overwhelming sepsis and lobar pneumonia. Leukopenia without a disproportionate reduction of granulocytes is common in a number of infections. Hence, leukopenia with granulocytopenia alone in an infectious process cannot be made a basis for a separate classification.

In connection with the view that it is simply a leukopenic reaction to an unusually virulent general infection, it seems desirable to note briefly the principal conditions in which leukopenia may appear. The term leukopenia is applied to the presence of a subnormal number of leukocytes per cubic millimeter of blood and may properly be used if the leukocyte count falls to less than 5,000 per cubic millimeter. Leukopenia may occur in a wide variety of conditions<sup>38</sup>. Among the most common are the following: starvation, chronic intoxications, particularly those due to lead, arsenic, thorium, benzene, mercury, alcohol, ether or morphia, irradiation with roentgen rays, diseases of the blood or blood-forming organs, notably primary pernicious anemia, aplastic anemia and aleukemic leukemia, Banti's disease, certain infections, notably dengue fever, kala azar,<sup>39</sup> measles, influenza, glanders, malaria, typhoid fever, certain cases of fulminant septicemia and lobar pneumonia. The discovery of leukopenia is often of value as an aid to diagnosis in typhoid fever and influenzal infections.

Leukopenia coincident with or following severe infections has been noted frequently. Menninger<sup>40</sup> reported a case of lobar pneumonia with a leukocyte count ranging from 150 to 275 per cubic millimeter, with 5 per cent neutrophils and 95 per cent lymphocytes. Naegeli<sup>41</sup> stated that leukopenia occurs in from 5 to 10 per cent of cases of lobar pneumonia. Chatard,<sup>42</sup> in a study of 582 cases of lobar pneumonia, found 2,500 leukocytes per cubic millimeter to be the lowest count occurring in the series. Lanford<sup>43</sup> saw a case of lobar pneumonia with an initial leukocytosis of 17,000, 88 per cent of which were neutrophils. In six days the count had dropped to 800, with 40 per cent neutrophils.

In 1923, Sison and Lara<sup>44</sup> reported three cases of severe infection, all of which showed a marked degree of leukopenia and terminated fatally. In each case the neutrophils were particularly reduced, in one case to the point of disappearance.

Nakayama<sup>45</sup> discussed the production by streptococci of a toxin capable of destroying leukocytes. Weiskotten, Gibbs and Templeton<sup>46</sup> produced leukopenia in rabbits with benzene.

In infections such as lobar pneumonia and septicemia, the total number of leukocytes per cubic millimeter is considered roughly indicative of the patient's resistance, and the percentage of neutrophils has been thought to vary with the

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38 French, Herbert. Index of Differential Diagnosis, New York, William Wood & Company, 1921, p. 361.

39 Stitt, E. R. Practical Bacteriology, Philadelphia, P. Blakiston's Son & Company, 1923, p. 263.

40 Menninger, W. C. Extreme Leukopenia in Lobar Pneumonia, J. A. M. A. **85** 435 (Aug. 8) 1925.

41 Naegeli, O. Blutkrankheiten und Blutdiagnostik, Berlin, Julius Springer, 1923, p. 489.

42 Chatard, J. A. The Leukocyte Count in Acute Lobar Pneumonia, Johns Hopkins Hosp. Rep. **15** 89, 1910.

43 Lanford, J. A. Discussion of Paper, New Orleans M. & S. J. **75** 656, 1923.

44 Sison, A. G., and Lara, C. B. The Ominous Significance of Leukopenia with Either Absolute or Relative Lymphocytosis in Severe Infections, J. Philippine Islands M. A. **3** 291, 1923.

45 Nakayama, Y. On the Toxin for Leukocytes Produced by Streptococci, J. Infect. Dis. **27** 86, 1920.

46 Weiskotten, H., Gibbs, E., and Templeton, E. The Action of Benzol, J. M. Research **41** 425, 1920.



severity of the infection. A reduction of the lymphocytes is considered by Jones and Brown<sup>47</sup> as prognostically unfavorable, an increase augurs well.

Two principal theories concerning the mechanism of leukopenia<sup>48</sup> have been advanced, which are (1) that leukopenia is due to actual destruction of circulating leukocytes or their progenitors in the leukopoietic centers, and (2) that leukopenia follows the sifting out or accumulation of large numbers of leukocytes in various capillary beds, thus reducing the leukocyte content of the circulating blood.

Clinical and experimental evidence can be found to support both views, and it is possible that both types of mechanism are operative in many cases. Evidence of damage to bone marrow has often been demonstrated in severe infections,<sup>49</sup> and in such instances reduction of neutrophils might reasonably be expected. Wells<sup>50</sup> made careful leukocyte counts in different areas during a period of leukopenia following bacterial injections. Organisms were found in the liver and spleen soon after injection, and in these organs a leukocytosis occurred which was synchronous with a leukopenia of the peripheral circulating blood. The general leukocytosis which followed was assumed to result from the outpouring of leukocytes from the marrow centers to replace those drawn from the circulating blood. If a steady progressive drop in the number of leukocytes occurs, leukocytic destruction must be taking place.

2 As Mouzon<sup>51</sup> pointed out, the multiplicity and variety of the necrotic foci speak against specificity of the angina. Furthermore, necrotic anginas occur in aplastic anemia, primary pernicious anemia, acute leukemias, hemorrhagic purpura, arsenic poisoning, in patients cachectic from chronic disease or malnutrition, and in staphylococcal or streptococcal septicemias. Similar processes often occur unassociated with other disease and without leukopenia. Some advocates of the specificity of "agranulocytosis" (Friedemann<sup>51</sup>) believe the blood picture to follow the reaction of the hematopoietic system to a specific amygdalo-pharyngeal infection. As Mouzon observes, however, the necrotic angina often appears after the onset of the infection.

3 Epidemicity of the condition has not been reported.

4 Although most of the cases reported at first occurred in middle-aged women and this was considered an added argument for specificity, numerous cases have since been reported in males, and the age groups have shown a wide variation.

47 Jones, W. C., and Brown, C. E. The Clinical Significance of Total and Differential Leukocyte Counts with Special Reference to Acute Infections, *Am J M Sc* **164** 553, 1922.

48 Werigo, Lowit, M., Goldscheider, and Jacob, quoted by Drinker, C. K. *Oxford Med* **2** 560, 1920.

49 Muller, E. F. The Bone Marrow in Acute Infections, *Med Klin* **17** 1238, 1921.

50 Wells, C. W. Leukopenia and Leukocytosis, *J Infect Dis* **20** 219, 1917.

51 Friedemann, U. Agranulocytic Angina, *Med Klin* **19** 1357, 1923.

5 A variety of organisms has been recovered from the blood stream and local (oral) lesions, in many instances pathogenic organisms have not been found. Thus a constant etiologic agent has not been established.

6 Aside from the practically constant oropharyngeal lesions, the visceral changes reported are not consistent, and in some instances significant organic lesions have not been found.

7 Satisfactory experimental reproduction of the condition with material from affected patients has not been accomplished.

In view of these facts it does not seem justifiable to classify this condition as a distinct or specific pathologic entity, and the burden of proof would appear to rest on those who consider it as such. In the light of present knowledge, or lack of knowledge, concerning any specific etiology, it does not seem reasonable to regard so-called agranulocytosis as anything more specific than a type of reaction on the part of the leukopoietic system, or that portion of it concerned with the production of granular leukocytes, to an infection so overwhelming as to destroy the neutrophils and paralyze their centers of production. We would submit the aforementioned reasons in support of this view.

The use of the terms "agranulocytosis" and "agranulocytic angina" we regard as particularly unfortunate. Such terms imply a specificity which not only remains unproved, but appears unlikely. Furthermore, the suffix "osis" is not applicable in reference to a disease or morbid process affecting the nongranular leukocytes, as the term "agranulocytosis" would imply. For the present at least, the use of a descriptive term, such as "sepsis with granulocytopenia," or "agranulocytic infection," as suggested by David<sup>52</sup> and Feer,<sup>53</sup> would appear more desirable.

#### CONCLUSIONS

The available evidence does not justify a conception of so-called agranulocytosis or agranulocytic angina as a specific disease entity. On the contrary, the known facts concerning the reported cases would indicate that the picture produced is the result of a nonspecific reaction to an infection of unusual absolute or relative virulence, and that a variety of infecting organisms may possibly play a part in its production.

The continued use of the terms "agranulocytosis" and "agranulocytic angina" seems undesirable in view of their implication of specificity. Substitution of a more general descriptive term, such as "sepsis with granulocytopenia" or "agranulocytic infection" is suggested.

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52 David, W. Agranulocytosis, *Med Klin* **20** 1614, 1924.

53 Feer, W. A Contribution to the Question of Agranulocytosis, *Schweiz med Wchnschr* **56** 551, 1926.

*Note* Since this article was written, our attention has been directed to two additional contributions on the subject (1) Stillman<sup>54</sup> reported two cases of the condition described, giving the data from the autopsy in both, and (2) Dasse<sup>55</sup> reported one case in which an autopsy was not performed. In all three cases, *B. pyocyaneus* was recovered from the blood stream. This brings the total number of cases described at present to eighty-one.

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54 Stillman M Clin North America **12** 805 (Nov ) 1928

55 Dasse, H W Agranulocytic Angina, J A M A **91** 1718 (Dec 1) 1928

# THE DISCORDANT ELECTROCARDIOGRAM †

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The QRS complex represents the excitation wave in the ventricles, and it is normally upright in both the axial and the transverse leads. Under certain conditions it has a downward direction in one of the leads. When this is the case, discordant curves are present as opposed to the normal, concordant curve. In the absence of other abnormalities, discordance by virtue of a downwardly directed QRS in the transverse lead is right axis deviation or preponderance and discordance of the opposite type is left axis deviation or preponderance.

In a simple strip of mammalian heart muscle with parallel fibers the electrical curves inscribed vary in form and direction in accordance with alterations in the position of the leading electrodes with reference to the muscle, although the direction in which the excitation travels and the line of the leading remain unaltered<sup>1</sup>. Since the form of these curves resembles the common variations in the form of the extrinsic curve, or the electrocardiogram of the intact heart, it may be that the latter is essentially an inscription of the electrical events along the line of the lead through which it is taken. This is also suggested by effects resulting when the line of leading is varied in hearts with localized injuries, and it can be explained by the fact that the potential differences influencing the electrocardiogram are diminished in the influence they exert on it in proportion as the direction in which they are developed recedes from the parallel with the line of the lead and approaches a perpendicular to it. If this were its only cause discordance would have a physical rather than physiologic basis, and would concern the relation between the position of the leads and the projection of the electrical axis on the line of the leading.

Although consideration of the conditions determining the electrical registration of the contraction wave in simple muscle strips indicates that an initial rapidly written upright deflection will occur whenever the wave of negativity indicating contractile activity begins nearest the negative pole of the galvanometer and moves in the direction of its positive pole and has a downward direction when the reverse is the case, it is not the direction of the movement of the excitation which

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† From the Laboratory of Physiology, Faculty of Medicine, Paris.

1 Craib, W. H. A Study of the Electrical Field Surrounding Active Heart Muscle, *Heart* **14** 71, 1927. Taussig, H. B. Electrograms from Isolated Strips of Mammalian Ventricular Cardiac Muscle, *Bull. Johns Hopkins Hosp.* **43** 81, 1928.

actually determines the direction the deflection will take, but the temporal and quantitative relations of the excitation to the poles of the galvanometer. If an excitation begins simultaneously at both ends of a muscle strip connected to the poles of a galvanometer, developing an equal amount of potential difference at both points, there will be no effect on the instrument, and if one precedes the other by a small interval the principal deflection of the curve is in one direction, and reversing the precedence in excitation order causes the primary deflection of the curve to take the other direction. On the other hand, simultaneous excitation at both ends of a strip, when the potential developed at one end outweighs that in the other end causes the deflection to follow the excitation which is associated with the greater volume of negative poten-

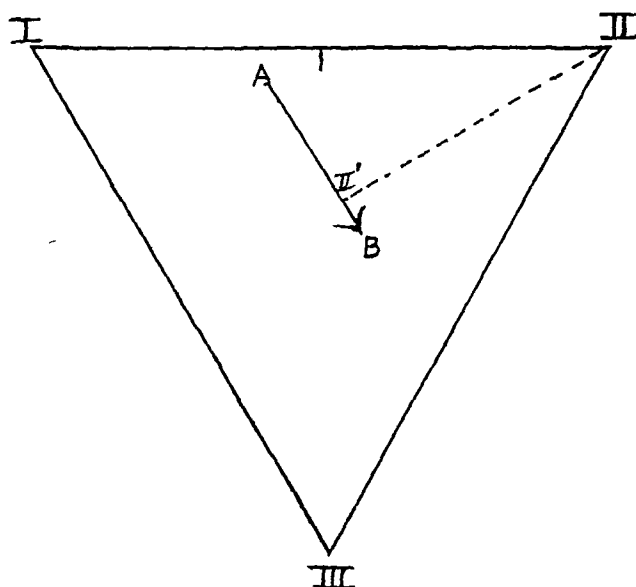


Fig 1—I, II and III represent the points of the lead according to the Einthoven schema, A-B, the electrical axis of the heart

tial difference. It follows that an excitation within the heart may be moving in the opposite direction to that suggested by the direction of the principal deflection of the string. This has actually been demonstrated by Craib.<sup>2</sup> The doublet hypothesis<sup>2</sup> can explain discordance as it is observed clinically by assuming that alterations in the form or direction of the curve taken with the usual deviations, I, II and III, may be the result of a change in the relation between the points of the leading and the electrical axis (the line along which the potential is developed), the direction of the leading being unchanged. Thus in figure 1 the points from which the leads are taken are represented as I, II and III, and the difference of potential is developed along the line AB, in that direction

2 Craib (footnote 1, first reference)

Although the accepted conception indicates that concordant curves would be present, if it is assumed that the closest electrical proximity of the electrodes *II* and *III* happens to be at points *II'* and *B'*, conditions exist for the appearance of discordance, since in derivation *III* the curve will have an initial deflection which has a downward direction. This explanation, however, requires a double assumption that the curve mainly represents the electrical events which have occurred along the line of the leading which is in keeping with the facts, and secondly, that the events of excitation within the heart are simple, which is less so.

When the question is simplified by omitting the implications of the doublet hypothesis, and the assumption is held that the electrical relation of the electrodes of the lead is to the ends of the electrical axis, discordance may be caused in two ways—an altered position of the heart with reference to the electrodes or an alteration of the excitation within the ventricles.

In the experimental observations on the subject, no disagreement exists between the observations made on animals and on man with regard to the appearance of concordant or discordant electrocardiograms, except in the case of bundle branch block.<sup>3</sup> Normal electrocardiograms obtained from man and animals with the usual method of leading present concordant curves, and the discordant curves obtained in man, i. e., the curves of preponderance or axis deviation, are duplicated in normal hearts by shifting the position of the heart within the thorax in the experimental animal<sup>4</sup> or the equivalent shifting of the position of the electrodes for the leading in man,<sup>5</sup> and, therefore, are due to a shift in the position of the heart with reference to the leads used in taking the curve.<sup>6</sup> In the case of right bundle branch block, a discrepancy is present. The curves in this condition in man are mostly discordant, with the initial deflection downwardly directed in the axial lead, whereas concordant curves are commonest in the experimental animal. Since there are only two cases recorded with evidence for the location of the point of injury,<sup>7</sup> the anatomic comparison cannot be made

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3 Lewis, T. The Spread of the Excitatory Process in the Vertebrate Heart, Phil Tr Roy Soc London **207** 221, 1916. Wilson, F. N., and Herrmann, G. R. Bundle Branch Block and Arborization Block, Arch Int Med **26** 153 (Aug) 1920, Heart **9** 91, 1922. Wilson, F. N., and Herrmann, G. R. Ventricular Hypertrophy, Heart **9** 91, 1922.

4 Meek, W. J., and Wilson, A. The Effect of Changes in Position of the Heart on the QRS Complex of the Electrocardiogram, Arch Int Med **36** 614 (Nov) 1925.

5 Cohn, A. E. An Investigation of the Position of the Heart to the Electrocardiogram, Heart **9** 311, 1922.

6 Alteration in the excitation may also result in discordance (figs 2 and 3).

7 Eppinger, H., and Stoerk, O. Zur Klinik des Elektrokardiograms, Ztschr f klin Med **71** 157, 1910.

between the effects in dog and in man to explain the difference in the curves

Lewis<sup>8</sup> noted in the dog that discordance in experimental bundle branch block, when it occurred, was not due to a difference in the position of the heart with reference to the leads used or similar factors, but occurred in hearts in which the initial upright deflection was of large amplitude and presented less bridging of the cavity of the left ventricle by subdivisions of the left branch than in hearts with concordant curves. Rothberger and Winterberg<sup>9</sup> investigated the effects of cutting the smaller branches of the bundle of His and found when the right branch of the bundle was the sole intact portion of the conduction bundle the initial deflection was upright in both leads, when the anterior division of the left bundle was the only functioning strand the QRS was upright in the axial lead and downwardly directed in the transverse lead and when it was either the posterior division of the left bundle or the bundle strands to the apex (Spitzernfasern), the reverse occurred. They also observed that section of the anterior division of the left branch of the bundle tended to produce an increase of S in the axial lead, whereas section of the posterior division had the opposite action. They concluded that the right side of the heart normally received the excitation from the right bundle and also the left anterior bundle and the apex from the left posterior branch of the bundle. Regarding the relation of the observations to the discordant curve of branch block in man, they reserved their opinion.

In the heart of the dog the bundle of His leaves the top of the septum and emerges on its surface in three main subdivisions, one of which appears on the right side as the right branch of the bundle and the other two on the left side to comprise the left branch. The latter leave the septum and pass to the anterior and posterior papillary muscles, breaking up into the network of Purkinje as they do so. The fine and compact strand of the right bundle pursues a longer course on the right face of the septum before it passes to the papillary muscle in the right chamber. There is great variation in the details of the division and distribution of these branches from animal to animal. In the human heart the conditions are the same save that the distinctive divisions of the bundle are not compact, but broad, flat and thin and advance fanwise.<sup>10</sup>

<sup>8</sup> Lewis (footnote 3, first reference)

<sup>9</sup> Rothberger, C. J., and Winterberg, H. Experimentelle Beiträge zur Kenntnis der Reizleit., Ztschr f d ges exper Med 5 264, 1916-1917

<sup>10</sup> Holl, M. Makroskopische Darstellungen des AV Bündel von Mensch und Tier, Arch f Anat u Physiol Anat Abt 1912, p 62

Twenty-eight experiments were made on the dog<sup>11</sup> to ascertain the effect of section of the three subdivisions of the His bundle on the electrocardiogram of the axial and transverse leads. They differed from those employed by Rothberger and Winterberg only in that the axial lead was right fore-leg to left hind-leg instead of anus to esophagus, and the transverse lead was carefully placed at the perpendicular to the axial lead. The results were like those of Rothberger and Winterberg, furthermore, section of the posterior or descending division of the left

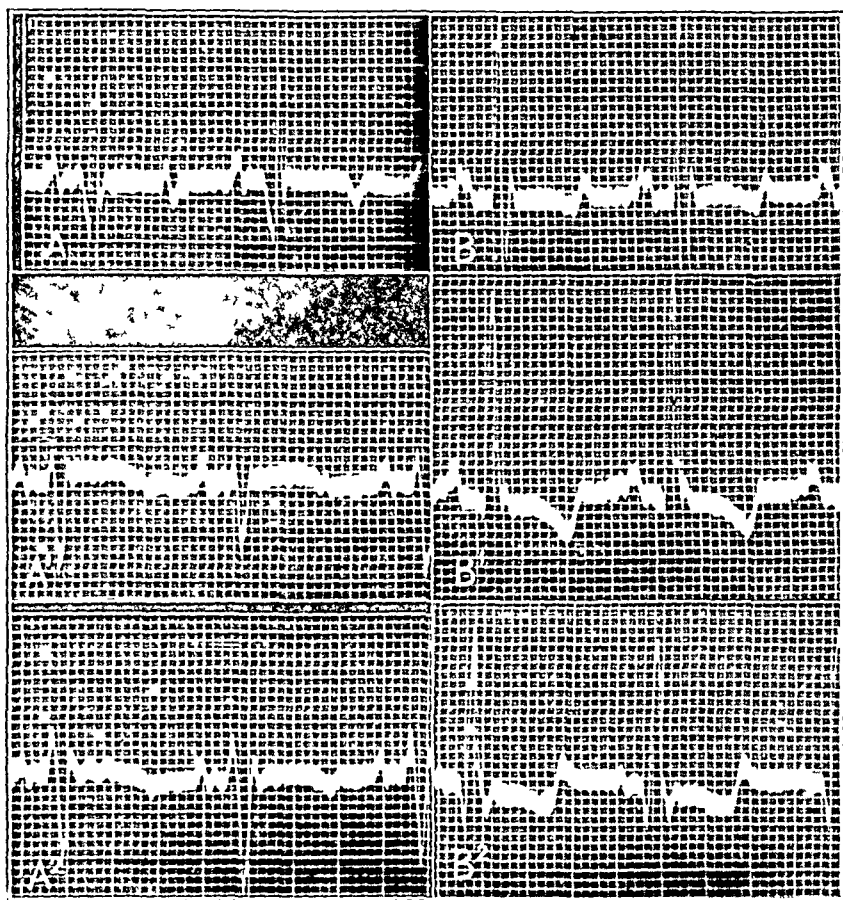


Fig 2—Electrocardiograms of the heart of a dog, time in fiftieth seconds *A*, transverse lead, *B*, axial lead, *A*<sup>1</sup>, *B*<sup>1</sup>, the same after section of the posterior division of the left branch of the bundle. The QRS changes in form although a normal QRS time persists. *A*<sup>2</sup>, *B*<sup>2</sup>, after section of the right branch of the bundle. Discordant branch block curves are present.

bundle not infrequently caused the main deflection to become downwardly directed in the transverse lead, associated with an increase in the height of R in the axial lead (fig 2) and the section of the anterior

11 The animals were anesthetized with chlorotone, the vagi were cut and artificial respiration instituted and the heart exposed by removing the sternum. The transverse lead corresponded to I, II and the axial lead to II and III of the electrocardiogram of man.



division of the left bundle, exactly the reverse, i e , it caused a negative QRS in the axial lead and an increase in the height of R in the transverse lead (fig 3) The section of these divisions of the left bundle in the presence of right branch block caused concordant curves associated with right branch block to become discordant When the posterior division was cut, the axial lead caused the discordance, it became upright, and when the anterior division of the left branch was cut, the transverse lead did so (figs 2 and 3)

In view of the precise conditions which determine the appearance of discordance in the group of experimental animals with concordant curves in right branch block, it would not be unreasonable to imagine that discordance in the curve of branch block in man has its origin in the presence of an injury to the His bundle which

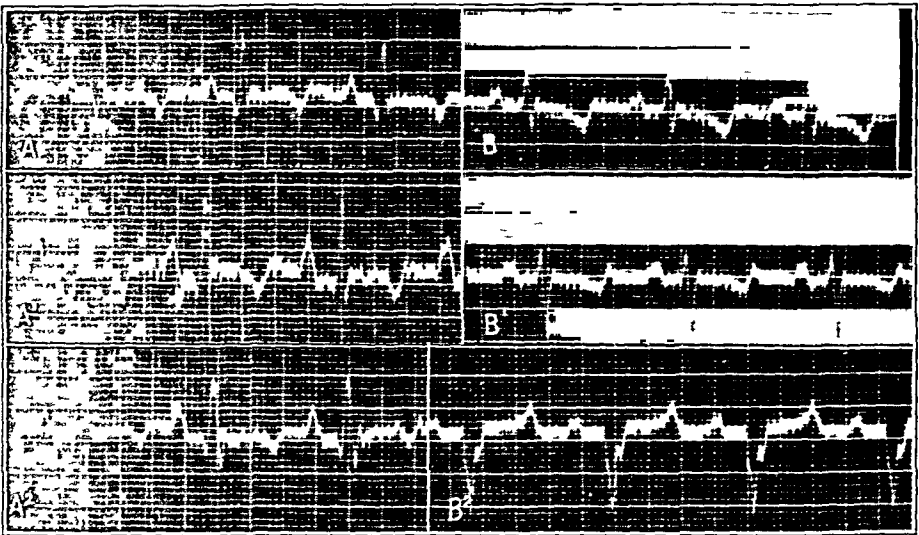


Fig 3—Electrocardiograms of the heart of a dog, time in fiftieth seconds *A*, transverse lead, *B*, axial lead, *A'*, *B'*, the same, following section of the anterior division of the left branch of the bundle, *A''*, *B''*, after section of the right branch of the bundle Discordant branch block curves opposite in character to those following the section of the posterior division of the left branch of the bundle are present

involves the right branch completely (since complete involvement of one branch is necessary for the appearance of a significantly prolonged QRS time) and the left branch incompletely, the nature of the discordance depending on the portion of the left branch of the bundle involved when the anterior division is involved, the discordance is due to an upright initial deflection in the transverse lead (i e , L I is upright), when the posterior division is involved, the discordance is due to an initial deflection upright in the axial lead (L III is upright) This theory would seem plausible were it not that the concordant curves

of branch block in the experimental animal may be converted into discordant curves by an alteration in the position of the heart just as is the case when the conduction is entirely normal

In the normal heart, the excitation travels to the myocardium by a threefold pathway. The areas of the heart muscle first receiving the excitation differ in their position with regard to the points of the leading and the electrical proximity they bear to the electrode associated with the negative pole of the instrument, which are the factors which will determine the direction taken by the deflection. As the principal deflection is normally upright in both axial and transverse leads, the direction of potential difference is from above down and right to left. The same holds true if the left bundle is cut, since the concordance remains, but when the right bundle is severed, the direction of potential difference is from below up and left to right, since the concordance is reversed. If the posterior division of the left bundle is now severed the axial lead becomes upright, after section of the anterior division of the left bundle on the other hand, the transverse lead becomes upright. It may be inferred, therefore, that the posterior division of the left bundle causes the direction of the potential difference to be from below up, whereas the anterior division has the reverse effect. Since the right bundle is a single strand with an influence on the electrocardiogram of the dog which is readily discerned, and the main features of the anatomic arrangement of the bundle of His in man and the dog are alike,<sup>10</sup> the use of leads from the chest may enable one, by eliminating the other causes for discordance, to apply to diagnosis by the electrocardiograph the difference which is due to the branching of the left division of the bundle.

#### SUMMARY

Discordance in the electrocardiogram when bundle branch block occurs in man is due to causes which may be physical or physiologic. The former is represented by an altered relation between the points of the lead and the ends of the electrical axis in the manner suggested by the doublet hypothesis or alteration of the position of the heart with reference to the points of the leading, the latter, by the influence of the two main divisions of the left branch of the His bundle on the form of the electrocardiogram.

# OPIUM ADDICTION

## III THE CIRCULATION AND RESPIRATION OF HUMAN ADDICTS DURING THE ADMINISTRATION OF MORPHINE \*

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AND  
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The data presented in this paper have been accumulated from the study of a number of opium addicts for the purpose of determining whether prolonged addiction to the drug or its derivatives has brought about any detectable changes in the behavior of the circulatory system. We have studied the heart and circulation not only while the addict was at rest in bed but when he was subjected to a standardized physical task. As a basis for comparison, similar tests were conducted on trained and untrained persons not addicted to opium. This paper also includes an electrocardiographic study as well as orthodiagrammatic measurements of addicts while morphine was being administered. It also contains the effects of the injection of atropine sulphate on the heart rate and P-R interval in a series of addicts while they were receiving morphine.

### EXPERIMENTAL PROCEDURE

All the experiments and measurements were performed during the morning, usually between 9 and 12. The addicts were not given any breakfast when studies were to be made. In all cases, the subjects were receiving morphine at regular intervals, the amounts ranging between 6 and 28 grains (0.4 and 1.82 Gm) per day, enough to supply their needs.

The basal pulse rates, blood pressures and respiration rates were obtained after the subjects had been reclining in bed for half an hour.

The figures for the blood pressure are the average of as many as could be accurately taken in a period of five minutes. The figures for the pulse and respiration rates are the average of a continuous five minute count. The figures obtained while the addict was standing were always made following those obtained while he was reclining. Following this period, he was asked to stand quietly in the

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\* From the Narcotic Wards of the Philadelphia General Hospital

\* Expenses of this research were defrayed by the Committee on Drug Addictions, New York City. The research was carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction, in the wards of the Philadelphia General Hospital, which were placed at our disposal through the courtesy of the director of public health, city of Philadelphia.

erect posture, partially supported by the wall or window, and was not allowed to move except for a slight occasional shifting of the position of the feet. He was allowed to stand for five minutes, when again a series of determinations of blood pressure was made for a period of five minutes as well as a continuous count of the pulse rate, the figures were then averaged.

The electrocardiographic records before and after the injection of atropine were made for us by Dr. Thomas MacMillan, who is in charge of the electrocardiographic work in the Philadelphia General Hospital. The nine addicts selected for these tests were sent to this department without breakfast and rested in a chair for from fifteen to thirty minutes before records were made. Following the taking of the record after this rest period, each addict was given  $\frac{1}{20}$  grain (3 mg.) of atropine sulphate hypodermically, and records were taken every three or four minutes for the next hour and a half.

The staircase climbing test was carried out on addicts and nonaddicts, some of the latter were athletes in active training, members of the varsity crew and track teams of the University of Pennsylvania. The nonathletes were made up largely of interns from the Philadelphia General Hospital as well as of the members of the staff investigating this problem. None of the group of nonathletes was engaged in any form of systematic exercise, and all were leading a more or less sedentary life.

All subjects on whom the staircase climbing test was carried out, regardless of the group, abstained from breakfast and reclined in bed for thirty minutes before the basal blood pressure, and pulse and respiration rates were determined during a five minute period. They then walked slowly down the two flights of stairs. They were allowed to sit on the lower step for five minutes to rest preliminary to their climb. At the end of this five minute rest period, the climb was immediately begun, the subject being paced by one of the observers, each taking two steps at a time. A stop watch was used so that the length of time required to travel up the stairs was practically the same in all cases, varying from eighteen to twenty-one seconds. The task of climbing the fifty-four steps was arduous, because the time was so short that the subject was required to run at top speed, taking two steps at a time. As soon as the subject arrived at the top of the staircase, he lay down at once on the bed, and blood pressure, pulse and respiration rates were determined. Determinations of blood pressure were made continuously for five minutes, while a continuous record of the pulse and respiration rates was taken. The first determinations of blood pressure, pulse and respiration rates are recorded separately in the tables and charts. Following this, the blood pressures were averaged for each minute, and the respiration and pulse rates given per minute.

## RESULTS

In table 1 are summarized the figures for the blood pressures and pulse rates of a group of addicts, both while they were reclining and while they were standing, together with the respiration rate while they were reclining. Of the fifty patients whose pulse rate was studied while they were reclining, fifteen showed a rate between 50 and 60 a minute, twenty-four between 60 and 70, eight between 70 and 80 and three between 80 and 85. The individual pulse rates taken while the patients were standing were 1 case, below 60, four cases between 60 and 70, thirteen cases between 70 and 80, six cases between 80 and 90, five cases between 90 and 100 and one case at 112.

The range of systolic pressures while the forty subjects studied were reclining showed only one pressure below 100 mm, namely, 98 mm. In nine cases the pressures were between 100 and 110, in fifteen cases between 110 and 120, in twelve cases between 120 and

TABLE 1—*Blood Pressure, Pulse and Respiration Rate of Human Addicts During the Administration of Morphine*

	Pulse Rate		Blood Pressure		Respiration
	Patient Reclining	Patient Standing	Patient Reclining	Patient Standing	
Number of cases	50	30	40	28	43
Highest	84	112	138/92	138/89	22
Lowest	52	66	98/62	88/64	10
Average	65	79	117/72	108/74	18

130 and in three cases between 130 and 140. The systolic pressures obtained in twenty-eight addicts while standing were distributed as follows: in one case, between 80 and 90, in three cases, between 90 and 100, in sixteen cases, between 100 and 110, in three cases, between 110 and 120, in four cases, between 120 and 130, and in one case between 130 and 140. The determination of the diastolic pressures of the forty reclining subjects studied resulted in two between 50 and 60, sixteen between 60 and 70, sixteen between 70 and 80, and six between 80 and 90. Diastolic pressures taken while the subject was standing were between 60 and 70 in five cases, between 70 and 80 in fifteen cases, and between 80 and 90 in ten cases.

Of the forty addicts in whom the respiratory rate was studied while they were reclining, the rate of six fell between 10 and 15 per minute, of thirty between 15 and 20 and of fourteen between 20 and 22 per minute.

Table 2 contains a summary of the electrocardiographic studies of nine addicts together with the effects of the administration of  $\frac{1}{20}$  grain (3 mg) of atropine sulphate. The average pulse rate of these addicts was 75.8 per minute and the average P-R interval, 0.157 second. Both

auricular and ventricular complexes were normal in all the leads in all cases. Of the nine cases studied, the P-R interval in one case was 0.18 second, in three cases 0.16 second, in one case 0.15 second, in three cases 0.14 second, and in one case 0.13 second. The average decrease of the P-R interval due to the effects of the atropine sulphate was 0.26 second, the individual results being in one case, a decrease of 0.05 second, in two cases, 0.04 second, in two cases, 0.02 second, and in two cases, 0.01 second. The percentage increase in the rate after

TABLE 2—*Summary of Electrocardiographic Studies in Human Addicts During the Administration of Morphine Together with the Effects of the Administration of One Twentieth Grain of Atropine Sulphate*

No. of cases	Rate Before Atropine	Rate During Height of Atropine Effect	Per Cent Increase	Time of Greatest Effect	P R Interval Before Atropine	P R Interval During Height of Atropine Effect	Decrease in P-R Interval	Time of Greatest Effect
Highest	90	125	60	36 min	0.18	0.15	0.05	36 min
Lowest	74	81	21	16 min	0.14	0.11	0.01	7 min
Average	75.8	101.3	45.9	24.7 min	0.157	0.13	0.027	14.5 min

TABLE 3—*A Comparison of the Cardiac Response to Staircase Climbing as Shown by Pulse Rate in Human Addicts During the Administration of Morphine and in Athletes and Nonathletes*

	Basal	First Reading	First Minute	Second Minute	Third Minute	Fourth Minute	Fifth Minute
Addicts (22 tests)							
Highest	82	152	127	111	101	95	93
Lowest	51	92	77	62	56	55	59
Average	64	126	101	84	77	75	76
Athletes (11 tests)							
Highest	79	128	96	72	77	76	79
Lowest	56	110	78	50	50	52	56
Average	67	117	84	65	67	65	68
Nonathletes (10 tests)							
Highest	89	152	125	107	102	107	103
Lowest	61	104	82	62	60	62	74
Average	75	126	107	91	88	87	87

the administration of atropine, while averaging 45.7 per cent, was distributed as follows: in one case it increased to 21 per cent, in three cases between 30 and 40 per cent, and in four cases between 50 and 60 per cent. The time of the greatest effect of the atropine sulphate on the P-R interval averaged fourteen and a half minutes. Of the individual cases, one showed the greatest effect in seven minutes, two cases in nine and a half minutes, two cases in twelve minutes, and the rest distributed as follows, namely, fourteen minutes, twenty-two minutes and thirty-six minutes, respectively.

Figure 1 is a typical tracing obtained from an addict, a man, aged 26, who received 12 grains (0.78 Gm.) of morphine sulphate every twenty-

four hours His history of addiction extends over a period of eight years, during which time he claimed to have used as much as 25 grains (1.6 Gm) of morphine a day

Tables 3 to 6 inclusive contain the summaries of the response of the blood pressure, heart and respiratory rate to staircase climbing in a group of twenty-two addicts compared to these results for eleven athletes and ten nonathletes Comparison of the average pulse rate reaction in the groups shows that the initial increase in the rate of the addicts was 12 beats more than the rate of the athletes, and 11 more than that of the nonathletes At the end of the five minute observation

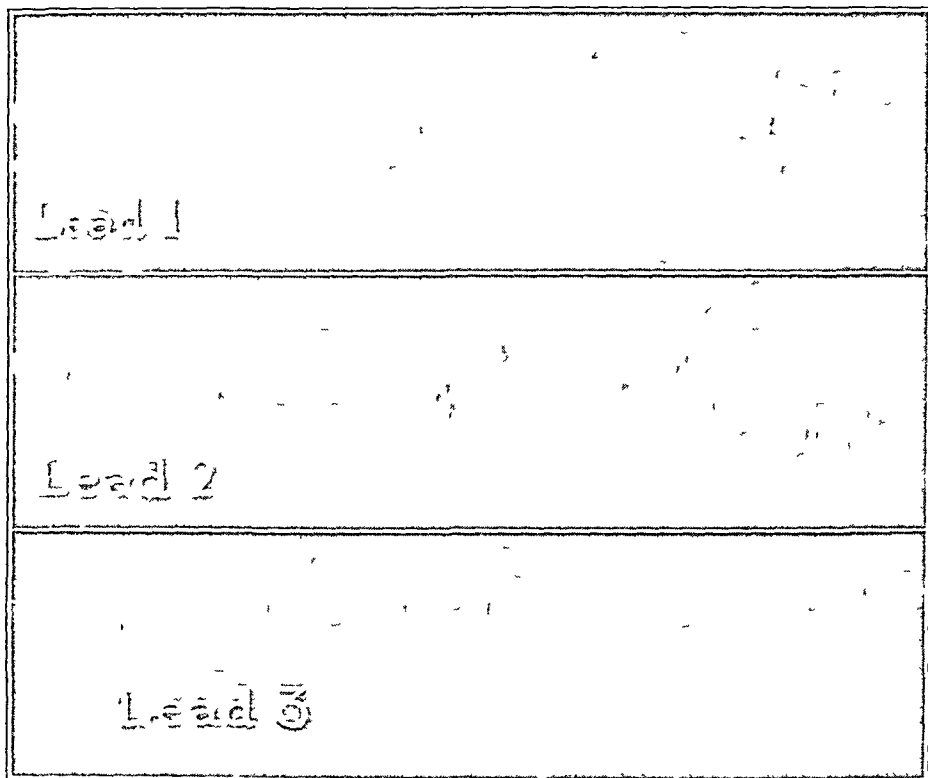


Fig 1—Electrocardiographic tracing obtained from a male opium addict, who has used morphine for eight years The daily dose in the ward was 12 grains (0.78 Gm) of morphine sulphate

period, the addicts' average rate was still 11 beats above the basal level, that of the nonathletes 12 beats and that of the athletes only one beat above their individual basal levels

The initial increase in systolic pressure was greatest in the athletes, namely, 45 mm, it was 33 mm in the nonathletes and 29 mm in the addicts At the end of five minutes, all three groups showed an average of 4 mm above the basal systolic pressure A comparison of the results of the determinations of the diastolic pressures showed an initial fall of 10 mm in the addicts, 22 mm in the nonaddicts and 10 mm

TABLE 4—*A Comparison of the Systolic Pressure Response to Staircase Climbing in Human Addicts During the Administration of Morphine and in Athletes and Nonathletes*

	Basal	First Reading	First Minute	Second Minute	Third Minute	Fourth Minute	Fifth Minute
Addicts (22 tests)							
Highest	135	176	180	164	151	138	131
Lowest	97	106	110	106	106	102	98
Average	116	145	146	141	132	125	120
Athletes (11 tests)							
Highest	138	178	180	165	148	139	132
Lowest	100	138	140	124	116	111	111
Average	119	164	160	145	132	126	123
Nonathletes (10 tests)							
Highest	135	168	178	160	151	139	138
Lowest	108	126	130	125	122	119	115
Average	116	149	150	141	134	123	124

TABLE 5—*A Comparison of the Diastolic Pressure Response to Staircase Climbing of Human Addicts During the Administration of Morphine and of Athletes and Nonathletes*

	Basal	First Reading	First Minute	Second Minute	Third Minute	Fourth Minute	Fifth Minute
Addicts (22 tests)							
Highest	82	80	80	80	79	83	81
Lowest	52	38	52	44	51	53	52
Average	70	60	63	64	64	64	64
Athletes (11 tests)							
Highest	77	80	70	82	78	78	75
Lowest	54	28	40	42	30	30	40
Average	66	55	60	62	60	59	61
Nonathletes (9 tests)							
Highest	91	74	78	73	75	79	77
Lowest	60	20	60	58	55	53	54
Average	70	52	74	63	74	72	74

TABLE 6—*A Comparison of the Response of Respiration to Staircase Climbing in Human Addicts During the Administration of Morphine and in Athletes and Nonathletes*

	Basal	First Minute	Second Minute	Third Minute	Fourth Minute	Fifth Minute
Addicts (22 tests)						
Highest	19	28	24	22	20	21
Lowest	12	17	14	11	11	13
Average	16	21	18	17	17	17
Athletes (11 tests)						
Highest	22	27	27	27	25	25
Lowest	10	14	11	11	10	10
Average	14	18	15	15	14	14
Nonathletes (9 tests)						
Highest	22	30	27	26	22	22
Lowest	11	19	16	15	13	13
Average	16	23	21	19	18	17



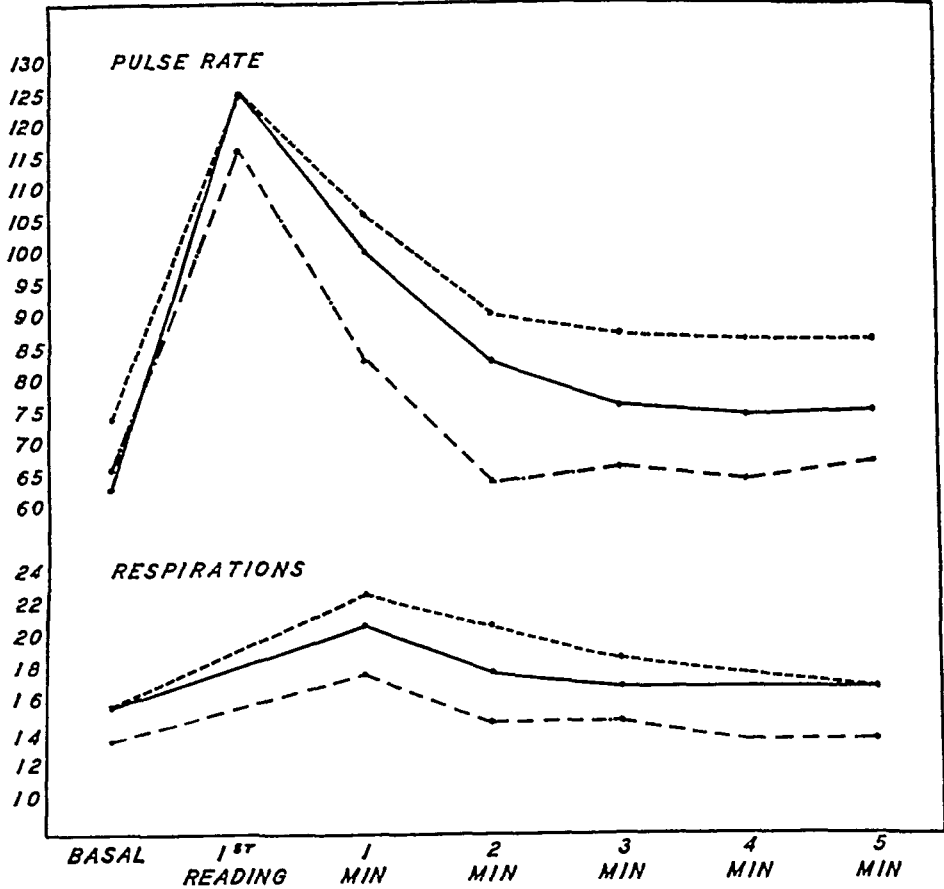


Fig 2—Average changes in pulse and respiration rates in a group of human addicts receiving morphine, nonaddicts and athletes, following the staircase climbing test. In this and fig 3, the solid line indicates addicts, the broken line, non-addicts, and the dash and dot line, athletes.

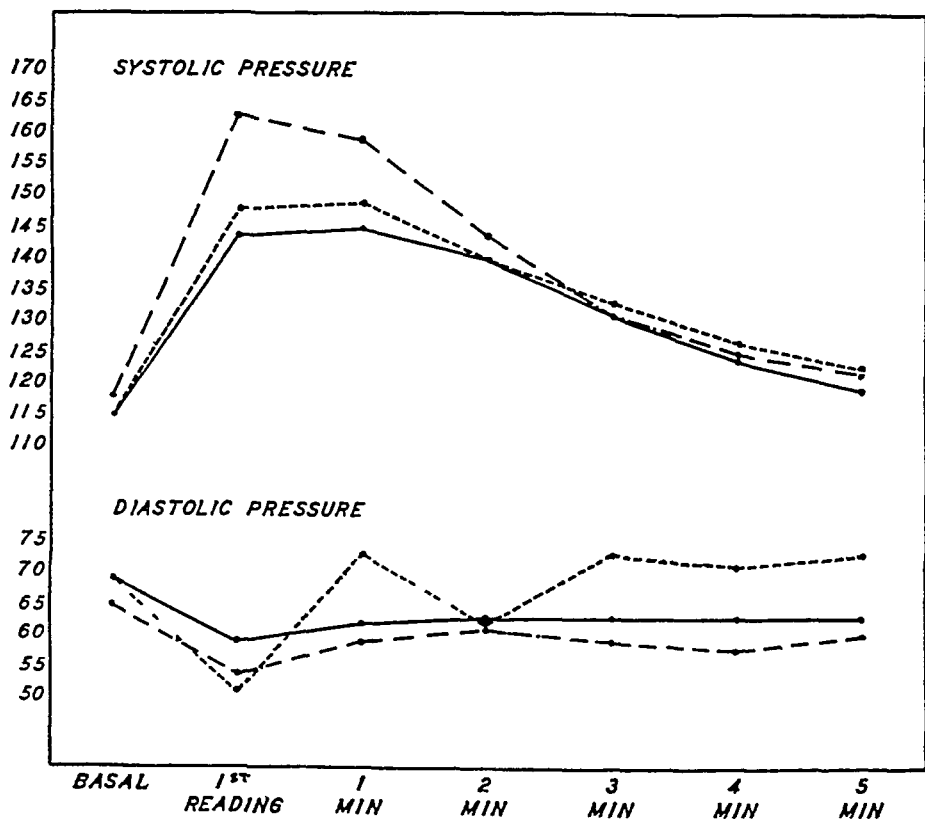


Fig 3—Average changes in systolic and diastolic blood pressure in a group of human addicts receiving morphine, nonaddicts and athletes, following the staircase climbing test.

in the athletes. At the end of the five minute rest period, the diastolic pressure of the athlete was still 5 mm below the basal pressure for the athlete, 4 mm above for the nonathlete and 6 mm below for the addict.

The changes in the respiratory rate showed an initial increase of 4 respirations per minute in the athlete, 7 in the nonathlete and 5 in the addict. Five minutes later, the average rate of the athletes was again normal, while those of the nonathlete and the addict were still one above.

The orthodiagrammatic measurements made of the heart of eight different addicts resulted in a range of the ratio of the transverse diameters of the heart to the chest of from 38.2 to 50 per cent. Of the eight cases in table 7, the ratios in four were within the normal range of Danzer,<sup>1</sup> namely, from 45 to 50 per cent. In three the ratio fell between 45 and 40 per cent and in one it was 38.2 per cent. All

TABLE 7—*Measurements of the Heart Obtained from Orthodiagram of Addicts During the Administration of Morphine*

Case Number	Aortic Arch, Cm	Transverse Diameters of Heart, Cm	Transverse Diameters of Chest, Cm	Ratio of Transverse Diameters, per Cent
26-32	4.1	11.5	28.3	40.6
26-31	5.0	12.9	26.0	49.6
26-21	5.6	12.3	27.8	47.8
26-35	5.4	12.6	26.8	43.2
26-31	4.1	10.8	23.2	38.2
26-30	5.2	12.3	28.1	43.7
26-39	4.5	15.3	31.0	49.3
26-29	4.8	13.1	26.2	50.0
Average	4.8	12.5	27.8	54.3

cases showed a diameter of the aortic arch of less than 6 cm, ranging from 4.1 to 5.6 cm, with an average of 4.8 cm.

#### COMMENT AND LITERATURE

A careful study of the data presented in this paper does not reveal any obvious deviation from the normal of the heart and circulation in human opium addicts during the administration of morphine sulphate to prevent withdrawal symptoms. The literature covering this subject in human addicts is limited to general statements regarding the circulation.

Levinstein,<sup>2</sup> one of the earliest writers on opium addiction in man, asserted that addicts frequently suffered with dyspnea and palpitation of the heart. He described the pulse as often being small and rather hard. Jouet<sup>3</sup> mentioned frequency of palpitation and precordial pain.

1 Danzer, C. Saul. The Cardiothoracic Ratio. An Index of Cardiac Enlargement, *Am J M Sc* **157** 513 (April) 1919.

2 Levinstein, Edward. *Die Morphiumsucht*, trans. by Charles Harrer, 1878.

3 Jouet, D. *Étude sur le morphinisme chronique*, These de Paris, 1883.

Bell<sup>4</sup> and Schwenninger<sup>5</sup> claimed the presence of fatty degeneration of the heart but Allbutt<sup>6</sup> did not believe this, because of evidence obtained at clinical examination or at autopsy. At an autopsy performed on an opium addict thirteen days after withdrawal of the drug, Ball<sup>7</sup> found slight myocardial degeneration but not sufficient to cause death. Pettey<sup>8</sup> believed in the presence of defective heart action, while Church and Peterson<sup>9</sup> included cardiac weakness, intermittence and bradycardia among the symptoms of opium addiction. Lambert<sup>10</sup> called attention to the slow pulse of the morphinist and stated that in the later stages there was a fall in arterial tension and enfeeblement of the heart. De Fursac and Rosanoff<sup>11</sup> claimed not only the occurrence of circulatory atony and weak cardiac impulse, but also of transient edemas in addicts. Sollman<sup>12</sup> and Anders and Musser<sup>13</sup> mentioned the frequent presence of cardialgia. Bishop<sup>14</sup> also called attention to the slow pulse of the morphinist. Sandoz<sup>15</sup> reported that addicts often complained of palpitation of the heart with rapid and irregular pulse accompanied with fainting spells. Legewie<sup>16</sup> studied the behavior in a case of morphine addiction from its inception to death. Despite attacks of delirium and motor excitations which could be relieved by additional amounts of morphine, at no time did the patient show any weakness of the circulatory system.

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4 Bell, F. M. *Morphinism and Morphinomania*, New York M. J. **93** 680, 1911.

5 Schwenninger, Ernst. *Gesammelte Arbeiten*, Berlin, 1886, vol. 1, chapter 4, pp. 143-151.

6 Allbutt, T. C. *A System of Medicine*, London, The Macmillan Company, 1908, vol. 2, part 1.

7 Ball, B. *Des lésions de la morphinomanie, et de la présence de la morphine dans les viscères, Encephale*, 1887.

8 Pettey, G. E. *Narcotic Drug Diseases and Allied Ailments*, Philadelphia, F. A. Davis and Co., 1913.

9 Church, A., and Peterson, F. *Nervous and Mental Diseases*, ed. 8, Philadelphia, W. B. Saunders Company, 1914, pp. 930.

10 Lambert, A., in Osler and McCrae. *Modern Medicine*, Philadelphia, Lea & Febiger, 1914, vol. 2, chapter 23, pp. 396.

11 De Fursac, Rogues J., and Rosanoff, A. J. *Manual of Psychiatry*, New York, John Wiley & Sons, 1916.

12 Sollman, Torald. *Manual of Pharmacology*, Philadelphia, W. B. Saunders Company, 1917, pp. 355.

13 Anders, J. M., and Musser, J. H. *Practice of Medicine*, Philadelphia, W. B. Saunders Company, 1920.

14 Bishop, E. S. *Morphinism and Its Treatment*, J. A. M. A. **58** 1499 (May 18) 1912.

15 Sandoz, C. E. *Report on Morphinism to the Municipal Court of Boston*, J. Crim. Law & Criminol. **13** 1 (May) 1922.

16 Legewie, B. *Delirium bei Morphinismus. Zugleich ein Beitrag zur Frage der Morphingewohnung*, Ztschr. f. d. ges. Neurol. u. Psychiat. **89** 558, 1924.

In a series of 96 patients in whom the behavior of the circulation was studied, not one complained of attacks of cardialgia. The history of the presence of palpitation was sometimes elicited when the addict was certain that he was not using sufficient quantities of the drug to prevent withdrawal symptoms. Two of the 96 cases showed occasional extrasystoles; otherwise irregularity of the pulse was never encountered. Normal figures for the basal pulse rate, blood pressure and respirations vary as shown in the literature. All the figures that we obtained, however, lie well within the normal variations. The average systolic blood pressure in a large series of normal subjects reported by Fisher<sup>17</sup> was 123.2 mm, while in 2,000 normal patients Schneider<sup>18</sup> found the systolic pressure, determined while the patient was reclining, to be 117.9 mm. Our average figure for the 40 addicts while reclining was 117 mm, identical with that of Schneider and 6 mm below the average in Fischer's cases, which may have included standing and sitting postures. Schneider's average for the pressure of the 2,000 normal men while standing was 120.2 mm; the average in our cases was 108 mm. Schneider attributed the fall in the systolic pressures when the subjects changed from reclining to standing postures to disease, unhygienic living or excessive cigaret smoking. An analysis of our cases revealed that 75 per cent showed a fall in the pressure when the patients changed from the reclining to the standing postures. All of these subjects were excessive smokers and lived rather unhygienic lives, however, this is true of practically all our addicts.

A comparison of Schneider's normal figures for the pulse rate while the patient is reclining, which he gives as 74.1, with those in our cases, which average 65 per minute, shows a slower rate for the addicts. Guy<sup>19</sup> however, in studying 100 normal subjects in the London Hospital gives an average figure of 66.6 beats per minute while the patient was reclining. Seventy per cent of the addicts we studied had a basal pulse rate below 70 per minute while reclining; this slightly slower than normal rate of the heart is in agreement with the figures of Lambert<sup>10</sup> and Bishop<sup>14</sup> for the pulse rate of morphine addicts and is suggestive of van Egmond's<sup>20</sup> theory that sensitiveness of the vagus

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17 Fisher, J. W., quoted by Norris, G. W., and Bazett, H. C. *Blood Pressure*, Philadelphia: Lea and Febiger, 1927, p. 127.

18 Schneider, Edward C., and Truesdell, Dorothy. *Am J Physiol* **61**: 429 (Aug.) 1922.

19 Guy. *Guy's Hosp Rep* **4**: 63, 1839, *Encyclopaedia of Anatomy and Physiology*, 1852, vol. 4, p. 186.

20 Van Egmond, A. A. J. *Ueber die Wirkung des Morphins auf das Herz (zugleich ein Beitrag zur Frage der Morphingewohnung)*, *Arch f exper path u Pharmacol* **65**: 197, 1911.

center to morphine is not lost. Schneider's average normal for the pulse rate while the patient is standing is 91.9 beats per minute, Guy's average normal is 78.9 beats per minute, while our average figure is 79 beats per minute. Our figures are therefore identical with those of Guy, but considerably lower than those of Schneider.

The average respiration rate of 18 per minute in the forty cases shows the striking absence of the pharmacologic action of morphine on respiration in addicts. There was no correlation between the amounts of the drug administered to these addicts and the individual variations in respirations.

The electrocardiographic tracings were analyzed and did not show fundamental differences from those obtained in a series of normal subjects in this hospital or from those published by Lewis.<sup>21</sup> In a study of the determination of the average P-R interval in normal patients, Lewis and Gilder stated that it is usually between 0.13 and 0.16 seconds. Our average figure for nine cases is 0.157 second, this figure being placed near their upper limits. Three of the nine cases showed P-R intervals above the average of 0.157 second, in one case, the interval was 0.18 second and in two, 0.16 second. We have no data at hand for comparison of the action of atropine in normal persons, but these results are given here as the same experiments were performed, and will be reported in a later paper, on the same subjects after the drug had been withheld for a period of six days.

Athletes were selected as one group for the study of the heart and circulation during the staircase climbing test with the object of obtaining a response which could be taken as representative of physical fitness for cardiac stress. Having obtained the reactions of the athletes, we had a basis for comparison with the addicts and untrained subjects. The response of the athletes was characterized by the greatest initial increase in systolic pressure, the least initial increase in pulse and respiration rate and the most rapid return to the normal figures. The response of the addicts compared favorably with that of the untrained nonaddicts in all respects except in the initial rise in pulse rate and blood pressure. The addicts met the strain of climbing the staircase with an increase in heart rate rather than with a rise in pressure. The readjustment to basal levels is carried out in the addict with as great rapidity as in the untrained nonaddict. The degree of perceptible dyspnea was far greater in the untrained normal subject than in the addict, who compared favorably with the athlete.

The data obtained from the orthodiagrammatic measurements of the chest suggest, that the heart of the addict is slightly smaller than the

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<sup>21</sup> Lewis, Thomas. *The Mechanical and Graphic Registration of the Heart Beat*, London, Shaw & Sons, 1920.

average as in four of our cases the ratio fell below the lowest limit of the normal ratios of Danzer,<sup>1</sup> namely, 45 per cent. Case 26-31, in which the ratio was 38.2 per cent, did not show the slightest evidence of tuberculosis, as is suggested in cases in which the ratio falls below 45 per cent. Neither did the other three cases present any evidence of tuberculosis. The average diameter of the aortic arch does not suggest any widening in these cases.

#### CONCLUSIONS

A study of the pulse rate and blood pressure while the subject is reclining and while he is standing, of the respiration, electrocardiograms and response to staircase climbing tests in a series of opium addicts, who were given morphine in sufficient quantities to prevent withdrawal symptoms, resulted in the failure to find marked deviation in the behavior of the circulation and respiration from that of normal persons.

The average pulse rate in 70 per cent of our patients while reclining was slightly below the usual average figures given for normal persons.

Orthodiagrammatic measurements showed a tendency for the heart of the addict to be smaller than the average heart in normal subjects.

## Book Reviews

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DISEASES OF THE GALL BLADDER AND BILE DUCTS By EVARTS AMBROSE GRAHAM, A B, M D, Professor of Surgery, Washington University School of Medicine, St. Louis, Surgeon-in-Chief, Barnes Hospital and St. Louis Children's Hospital, WARREN HENRY COLE, B S, M D, Instructor in Surgery, Washington University School of Medicine, Assistant Attending Surgeon, Barnes Hospital and St. Louis Children's Hospital, GLOVER H. COPER, A B, M D, Assistant Professor of Surgery Washington University School of Medicine, Assistant Attending Surgeon, Barnes Hospital and St. Louis Children's Hospital and SHERWOOD MOORE, M D, Professor of Radiology, Washington University School of Medicine, Director of Mallinckrodt Institute of Radiology, Radiologist to Barnes Hospital, St. Louis Children's Hospital, Shriners' Hospital and St. Louis Maternity Hospital Price, \$8 Pp 456, with 224 engravings and 8 colored plates Philadelphia Lea & Febiger, 1928

Other reviewers have pronounced this book superior to anything of its kind which has appeared since Rolleston's "Diseases of the Liver, Gall Bladder, and Bile Ducts" which was published in 1905. A comparison of the two is most interesting, for certainly there is no other book in the English language to which the new treatise may be likened. Rolleston devoted 182 pages to the group of subjects for which the present authors required 456. The striking part of the comparison, however, is not the number of pages or the quality of the material presented, for it is excellent in both, but rather the development in this particular field in a brief period of twenty-three years and the difference in the point of view. Rolleston describes in great detail the varied pathologic conditions of the biliary tract with their respective symptomatologies, and discusses so thoroughly and well the etiology, diagnosis, prognosis and treatment that his work remains authoritative. It definitely presents the attitude of that school the ambition of which it is to know thoroughly the subject of pathologic anatomy and to apply this knowledge at the bedside.

In the newer work the anatomic point of view has been replaced by a combined anatomic and physiologic one. Graham and his co-workers cannot be said to have neglected pathologic anatomy. In fact, they have made significant contributions to it, such as the establishment of the relationship between cholecystitis and hepatitis. The chapter on the "Pathogenesis of Cholecystitis" is splendid and marks a real advance in our views of the subject. But to this faithful presentation of morbid anatomy and its corresponding symptomatology there is added so much consideration of the functional that one is at once aware of the fact that emphasis is placed on the physiologic rather than on the anatomic. The fixed attitude of pathologic anatomy has been superseded by the active flexibility of experimental pathology and physiology. This change is noticeable throughout the book. A considerable amount of controversial material is included in the chapter on the "Physiology of the Gall Bladder," but this is essential for a comprehensive understanding of the subject, and the chapter is an excellent one.

The subject of radiology of the gallbladder is presented splendidly, a full 100 pages being devoted to it, which is none too much when one considers that its authors are the originators of the modern methods of visualization of the gallbladder, and that they are more familiar with its possibilities than any one else. A historical sketch is given, and the value of roentgen examination of the biliary tract prior to cholecystography is carefully considered. A knowledge of this is essential for the proper comprehension of the importance of the newer method. The technic of cholecystography is described in detail and the much debated question as to the interpretation of atypical observations is discussed. Various statistical reports pertaining to the diagnostic efficiency of the procedure are given. Perhaps the authors may be accused of overenthusiasms, but certainly they have

seriously considered the various criticisms offered and have not hesitated to accord equal value to the observations of others

It is something of a surprise to find a lengthy chapter devoted to tests of hepatic function, but, after reading it, one is glad to have had it included. Its rather large literature has been reviewed and presented in a clear manner together with the experiences and opinions of the authors. The same may be said of the chapters on surgical treatment in cholecystitis.

FUNGI AND FUNGOUS DISEASES. By ALDO CASTELLANI, M.D. Reprinted from the *Archives of Dermatology and Syphilology*, by the American Medical Association.

This book of 200 pages is a reconstruction of the Adolph Gehrman Lectures of the University of Illinois College of Medicine, delivered by Prof. Castellani in 1926, and published in the *Archives of Dermatology and Syphilology* between October, 1927, and March, 1928. It consists of three lectures: one on fungi, one on fungous diseases (referring to internal mycoses), and one on diseases of the skin due to fungi—the dermatomycoses. No one questions but that Castellani is an authority on the subject of mycoses.

The first lecture is extremely complicated, involving a nomenclature which is notoriously unstable in a field inadequately surveyed. Its contents are of invaluable aid to the intensive student in this field and to the mycologist as a reference work. The classification is so complex that as the introductory chapter to the volume, it may offer a rather formidable obstacle.

The subsequent two lectures, with their direct application to concrete clinical problems, have a different flavor and are informative and stimulating. The author's method of emphasizing the etiologic factor in the various fungous diseases, and of considering definitions, synonyms, clinical symptoms, illustrative cases and therapy, should make the book valuable, not only to the dermatologist but to the general practitioner as well. The book is plentifully illustrated with drawings, photographs and colored plates.

It is generally assumed that fungous diseases are of importance only to practitioners in the tropics. While it is true that the majority do occur there, students of this subject point to the increasing incidence of these diseases, not only in the southern latitudes of the United States, but also in the temperate regions. One cannot help but agree with Castellani that since the perfection of the science of bacteriology, mycology has been sadly neglected. Castellani's book offers an excellent aid in correcting this neglect.

TRABAJOS Y PUBLICACIONES DE LA CLINICA DEL PROF. PEDRO ESCUDERO.  
Price, \$12.00. Buenos Aires: El Ateneo, vol. 3, 1928.

This volume of nearly 600 pages, lavishly illustrated, maintains the same high standard set in the former publications of Escudero's clinics which have been reviewed in these pages. The methods pursued are those of the older clinicians. Painstakingly thorough studies of cases or series of cases are made. Every known laboratory aid is used, when necessary, experimentation on animals carries the problems further. What impresses the reader most, however, is the intensity of the clinical investigations.

Much of the material consists of the continuation of studies previously outlined in these book reviews. This comprises the more important parts of the volume. Escudero's papers on splenomegalies, latent diabetes and the relations of diabetes to other diseases.

Many cases of diabetes have been recognized in the preglycosuric stage. Interesting pathologic features are noted, especially in the skin. Methods of diagnosing latent hyperthyroidism are also described. This test is based on the changes in the pulse and the metabolic rate following the administration of thyroid extract.

Of especial note is the continuation of the studies of bone marrow in various blood dyscrasias. Biopsies are made by inserting a drill into the marrow under



a local anesthesia and making smears of the exuding fluid. It appears to be a safe method which can be used in the office and offers possibilities of much earlier diagnosis than studies of the blood permit.

**ASTHMA. ITS DIAGNOSIS AND TREATMENT.** By WILLIAM S THOMAS. Price, \$7.50. Pp 279, with 26 illustrations. New York: Paul B Hoeber, 1928.

The author of this work describes, without going too deeply into theoretic considerations, the modern methods employed in studying the asthmatic patient. He emphasizes the importance of detailed histories of cases and of a thorough study of the many possible etiologic factors before treatment is planned. He points out especially the technic and interpretation of skin tests with all animal and vegetable exposures, including, when indicated, bacterial cultures made from secretions, excretions and infected foci. The chapters on the preparation and uses of autogenous vaccines describe distinct advances in this form of therapy. Several forms of nonspecific treatment that are now in vogue are described, most of them being rightfully condemned or their use questioned. The cooperation of the otolaryngologist and the internist is properly stressed. More detailed descriptions of the technic of desensitization to plant and animal proteins and of the precautionary measures necessary for this form of treatment should have been given. The last chapter, entitled the "Causes of Disappointing Results," again emphasizes the value of thoroughness. If the practical suggestions given in this book were carefully followed, there would be fewer disappointed patients returning from various climates where they had been advised to go for relief from asthma.

**LABORATORY MANUAL OF THE MASSACHUSETTS GENERAL HOSPITAL.** By ROY R WHEELER and F T HUNTER. Price, \$1.75. Pp 101. Philadelphia: Lea & Febiger, 1928.

This is the second edition of this laboratory manual which was first published for the use of the interns and students in the Massachusetts General Hospital. It contains the usual procedures for routine laboratory work, and in addition has chapters briefly discussing special diagnostic procedures and the technic of the common therapeutic measures used in the hospital. The book is not intended to cover the material exhaustively, but to describe briefly how to carry out the different procedures quickly and accurately. The book accomplishes its purpose.

**BOOK OF DIETS OF THE MCGUIRE CLINIC AND ST LUKE'S HOSPITAL, DEPARTMENT OF DIETETICS, RICHMOND, VA.** Pp 50. 1928.

This is a pamphlet of fifty pages containing the diet used by the McGuire Clinic of Richmond for medical and surgical cases. On the whole it is good and will serve as a basis for future diets.

## THE BACTERIOLOGY OF THE BLOOD AND JOINTS IN CHRONIC INFECTIOUS ARTHRITIS<sup>†</sup>

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AND

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NEW YORK

This study deals with the etiology of a form of chronic arthritis which has been variously referred to as rheumatoid arthritis, arthritis deformans or chronic infectious arthritis Goldthwaite<sup>1</sup> and his school call it atrophic arthritis. It may be defined as a chronic inflammatory condition of the joints and periarticular tissues, characterized in the earlier stages by migratory swelling and stiffness of the joints, and in the later stages by more or less deformity and ankylosis. In the great majority of cases, several joints are involved, indeed, one of the most striking features of the disease is its tendency, if unchecked, to progress and finally to involve nearly every joint in the body.

The etiology of chronic deforming arthritis has long been a subject for debate. Perhaps no disease in the whole realm of internal medicine has been more prolific of hypotheses and theories. It has long been recognized that there were many predisposing factors, such as fatigue, cold and exposure, which played an important part in the actual onset of symptoms, but the exciting cause or agent has eluded the most persistent investigators.

The most important contribution to the etiology of chronic arthritis was that made by Billings<sup>2</sup> and his co-workers nearly twenty years ago, when they pointed out the relationship which existed between focal infection and chronic infectious arthritis. Other students of arthritis were quick to recognize the importance of this work, and now the rôle of focal infection in the etiology of this disease is widely recognized. Billings believed that the joint manifestations were nothing other than metastatic infections, and he preferred the term chronic infectious arthritis to arthritis deformans or rheumatoid arthritis.

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<sup>1</sup> Submitted for publication, Feb 15, 1929.

<sup>†</sup> From the Cornell Clinic and the Second (Cornell) Medical Division of Bellevue Hospital.

1 Goldthwaite, J E. Infectious Arthritis, Boston M & S J **101** 363 1904.

2 Billings, Frank. Chronic Focal Infections and Their Etiologic Relations to Arthritis and Nephritis, Arch Int Med **9** 484 (April) 1912.

In spite of the popularity of the theory of focal infection, modern authorities are not entirely in agreement as to the importance of such foci in the etiology of chronic infectious arthritis. Furthermore, even among those who accept the theory of focal infection, there is considerable disagreement as to what bacteria are actually responsible for the disease. The almost constant presence of various forms of streptococci in the original foci of infection has naturally led to the presumption that some type of streptococcus was responsible for the arthritic condition as well as for the focal infection. Unfortunately, the bacterial flora in the tonsils and about the teeth is so varied and contains such a multiplicity of streptococcal types that it has been impossible to determine whether *Streptococcus viridans*, *Streptococcus hemolyticus* or the indifferent streptococcus plays the etiologic part. This confusion is enhanced still further by the presence of just as many varieties of streptococci about the tonsils and teeth of healthy persons as in those patients suffering from chronic infectious arthritis.

McCrae<sup>3</sup> took the view that the condition is always secondary to a focal infection somewhere in the body, but doubted whether this means actual infection of the joint with organisms. He thought that the joint changes in many cases may be due to toxins. He ventured no opinion concerning the actual bacteria responsible for the disease.

Pemberton<sup>4</sup> expressed the belief that focal infection in the tonsils and teeth is responsible in many cases, but that a large variety of diseases of an infectious or inflammatory nature may act in an analogous way. He believed that the most important causative organisms are *Streptococcus hemolyticus* and *Streptococcus viridans*, "although probably any other organism is capable of producing the same results."

Osgood<sup>5</sup> stated that rheumatoid arthritis is a disease in which no specific organism has been found which can be held constantly responsible for its causation. He concluded that there are probably many different types of organisms and many other factors that play etiologic parts in its onset and course.

Nichols and Richardson,<sup>6</sup> after careful investigation of the pathologic changes in sixty-five cases of chronic arthritis, came to the conclusion that the lesions in the rheumatoid type might result from a great variety of origins, such as infection, disease and trauma.

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3 McCrae, T. Arthritis Deformans in Osler and McCrae. Modern Medicine, Philadelphia, Lea & Febiger 1915, vol 5, p 895

4 Pemberton, R. Arthritis in Nelson's Loose-Leaf Living Medicine, vol 5, p 605

5 Osgood, R. B. The Orthopedic Aspects of Chronic Arthritis, J Bone & J Surg 8 1 (Jan) 1926

6 Nichols, F. H., and Richardson, F. L. Arthritis Deformans, J M Research 16 149, 1907

Hench<sup>7</sup> of the Mayo Clinic expressed the belief that arthritis deformans is primarily of infectious origin. He emphasized the systemic nature of the condition.

A considerable amount of research has been carried out on the bacteriology of chronic infectious arthritis, but none of this can be said to have furnished conclusive information as to the exciting cause of the disease. The constant presence of various types of streptococci in the tonsils and about the teeth has naturally focused the interest of investigators on these organisms. Davis,<sup>8</sup> in 1911, took cultures from the various foci of infection which he found associated with chronic arthritis. In the great majority of cases, the hemolytic streptococcus was the predominating organism. With these streptococci, Davis was able to produce arthritis experimentally in rabbits. Blood cultures and cultures from the joint fluids of patients with chronic arthritis never gave positive results. However, Davis felt from his own investigations that the hemolytic streptococcus was probably the etiologic agent.

Working on the assumption that chronic deforming arthritis was a streptococcal disease, Hastings,<sup>9</sup> in 1913, resorted to the complement-fixation test as a method of determining which type of streptococcus was instrumental in causing the infection. By employing the old Wassermann technic, Hastings obtained positive complement fixation with the serum of arthritic patients and strains of streptococci isolated from foci of infection. In this way he believed that he could determine the exact biologic type of streptococcus with which the patient was infected.

More recently, Burbank and Hadjopoulos<sup>10</sup> have repeated Hastings' complement-fixation work with a slightly modified technic. They found that patients with periarthritic or deforming arthritis reacted positively to some form of hemolytic streptococcus, whereas patients with osteoarthritis reacted positively to streptococci of the *viridans* groups.

E. C. Rosenow<sup>11</sup> was disposed to look on *Streptococcus viridans* as the exciting agent in chronic infectious arthritis. This investigator

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7 Hench, P. S. The Systematic Nature of Chronic Infectious Arthritis, *Atlantic M. J.* **28** 425 (April) 1925.

8 Davis, D. J. Bacteriological and Experimental Observations on Focal Infections, *Arch. Int. Med.* **9** 505 (April) 1912, Chronic Streptococcus Arthritis, *J. A. M. A.* **61** 724 (Sept. 6) 1913.

9 Hastings, T. W. Complement Fixation Tests for Streptococcus, Gonococcus and Other Bacteria in Infective Deforming Arthritis and Arthritis Deformans, *J. A. M. A.* **60** 1208 (April 13) 1913, Complement Fixation Tests in Chronic Infective Deforming Arthritis, *J. Exper. Med.* **20** 52, 1914.

10 Burbank, R., and Hadjopoulos, L. G. Serologic Significance of Streptococci in Arthritis and Allied Conditions, *J. A. M. A.* **84** 637 (Feb. 28) 1925.

11 Rosenow, E. C. The Etiology of Arthritis Deformans, *J. A. M. A.* **62** 1146 (April 11) 1914.

took cultures from the enlarged lymph nodes of patients with chronic arthritis and was able to isolate *Streptococcus viridans* in a considerable number of cases

Small<sup>12</sup> believed that a certain number of cases of chronic infectious arthritis are nothing more than a chronic form of rheumatic fever, and as such are referable to infection with the indifferent streptococcus (*Streptococcus cardio-arthritis*)

From this review of the literature, it is evident that while bacteriologists have suspected the streptococcus as the exciting cause of chronic infectious arthritis, there is considerable disagreement among them as to which type or types of streptococcus are responsible for the disease

The natural and obvious place to look for the causal agent of chronic infectious arthritis is in the joints involved. Unfortunately, efforts to cultivate bacteria from the joints themselves have not been consistently successful

Rosenow,<sup>11</sup> in 1914, made cultures of the joint fluid in cases of chronic infectious arthritis and of the lymph nodes that drained the involved joints. He stated that in several instances he recovered "*Streptococcus viridans*" from both the glands and the joint fluid

Moon and Edwards,<sup>13</sup> in 1917, took cultures from the joints in ten cases of chronic infectious arthritis, and recovered a "non-hemolytic streptococcus" in six cases. They did not give any further description of the streptococci found

Richards,<sup>14</sup> in 1920, took cultures from the joints in fifty-four cases of chronic infectious arthritis, and isolated "*Streptococcus viridans*" in four cases

Billings, Coleman and Hibbs,<sup>15</sup> in 1926, took cultures from the joints in fourteen cases of chronic infectious arthritis. One yielded a "hemolytic streptococcus", five gave either a "non-hemolytic or a green producing streptococcus," and one gave a "mixed streptococcus culture with the non-hemolytic predominating." In six cases the results were negative, and in one the observations were not recorded

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12 Small, J. C. Rheumatic Fever. Observations Bearing on the Specificity of *Streptococcus Cardioarthritis* in Rheumatic Fever and Sydenham's Chorea, *Am J M Sc* **175** 638 (May) 1928

13 Moon, V. H., and Edwards, S. H. Results of Blood Cultures in Rheumatoid Arthritis, *J Infect Dis* **21** 154, 1917

14 Richards, J. H. Bacteriologic Studies in Chronic Arthritis and Chorea, *J Bacteriol* **5** 511, 1920

15 Billings, F., Coleman, G. H., and Hibbs, W. G. Chronic Infectious Arthritis. Statistical Report with End-Results, *J A M A* **78** 1097 (April 15) 1922

H Warren Crowe<sup>16</sup> took cultures from the joint tissue of five patients suffering from rheumatoid arthritis, and isolated a staphylococcus, *Micrococcus deformans*, in four of five instances. Control cultures from tissue removed from nonarthritic patients did not show this organism.

Forkner, Shands and Poston<sup>17</sup> recently took cultures from the joints in sixty-three cases of chronic infectious arthritis, recovering organisms in fourteen, or 22 per cent. Eleven of the joint cultures contained "*Streptococcus viridans*," two yielded gonococcus, and one, *Staphylococcus aureus*. Cultures of the lymph nodes draining the involved joints were made in twenty-one cases. Ten of these cultures were positive, nine showing *Streptococcus viridans* and one, gonococcus.

During recent years, several investigators have studied the bacteriology of the blood in rheumatoid arthritis.

Moon and Edwards,<sup>18</sup> in 1917, using Rosenow's technic, made blood cultures in eighty-three cases of rheumatoid arthritis, and recovered a "non-hemolytic streptococcus" in eighteen. They felt, however, that a diphtheroid bacillus, or *B. mucosus-capsulatus*, as well as the streptococcus, could act as the exciting agent in this disease. Moon and Edwards made no attempt to classify the streptococci which they isolated by sugars or immunologic tests. Furthermore, they did not report on nonrheumatoid conditions.

Richards,<sup>14</sup> in 1920, made blood cultures in cases of chronic arthritis, making use of North's medium. Blood cultures were taken in 104 cases of chronic infectious arthritis, and fourteen yielded positive results. Richards referred to the organism as "*Streptococcus viridans*," although he remarked that the character of the growth was not always typical, only three of his strains showing green in the original culture.

Hadjopoulos and Burbank<sup>18</sup> took cultures from the blood in 145 cases of chronic arthritis and obtained a streptococcus in fifteen (10 per cent). Nine of these strains produced hemolysis, while six were of the viridans type. In eight cases a diphtheroid bacillus was obtained, while five others showed *Staphylococcus aureus*. Hadjopoulos and Burbank do not give the technic employed other than to state that their success was due to "neutralization of alexin in the freshly drawn blood." No control cultures were reported. These investigators were able to produce an experimental arthritis in rabbits with their streptococci.

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16 Crowe, H. Warren. Bacteriology and Surgery of Chronic Infectious Arthritis, New York, Oxford University Press, 1927.

17 Forkner, C. E., Shands, A. R., and Poston, M. A. Synovial Fluid in Chronic Arthritis, Arch. Int. Med. 42: 675 (Nov.) 1928.

18 Hadjopoulos, L. G., and Burbank, R. A Preliminary Study Bearing on the Specific Causative Factors of Multiple Infective Arthritis, J. Bone & Joint Surg. 9: 278 (April) 1927.

Syranyi and Forro<sup>19</sup> recently took cultures from the blood in twenty-five cases of "polyarthritis" and obtained a streptococcus in 68 per cent. In nineteen of the cases described as "polyarthritis with fever," fourteen, or 73.6 per cent, were positive. In the remaining six cases in the group, referred to as "polyarthritis without fever," three, or 50 per cent, were positive. The organism isolated by Syranyi and Forro was classified as *Streptococcus viridans*. The various strains differed slightly in their reactions on the sugars, but they all fermented saccharose, salicin and lactose. These investigators did not report any experimental work on animals.

H. Warren Clowe<sup>16</sup> took cultures from the urine of patients suffering from rheumatoid arthritis and isolated a staphylococcus, *Micrococcus deformans*, in a high percentage of cases. *Micrococcus deformans* was not found in control cultures. He was unable to produce an experimental arthritis in animals with these staphylococci.

From this brief review of the literature, several conclusions seem justified.

- 1 While the relation of focal infection to chronic infectious arthritis is rather generally recognized, there is doubt in the minds of many as to whether the joint manifestations are actually metastatic infections or whether they are merely an expression of some toxic influence on the joint.

- 2 In respect to the bacterial agent responsible for the disease, a majority of the investigators look on the streptococcus as the exciting cause, but some believe that the staphylococcus, the gonococcus, the diphtheroid bacillus or some other micro-organism, as well as the streptococcus, can produce a deforming arthritis.

- 3 Even among those investigators who accept the streptococcus as a cause of rheumatoid arthritis, there is considerable disagreement as to which type of streptococcus is responsible, some considering it a *Streptococcus hemolyticus* infection, while others look on the indifferent or the green streptococcus as the causative agent. Another group of writers believes that deforming arthritis can be caused by any of the various types of streptococci.

- 4 A number of workers have found streptococci in the joints and even in the blood stream in cases of chronic infectious arthritis, but the results have been inconsistent and uncontrolled.

- 5 There has been little effort made to study the biologic relations between the streptococci which have been isolated from the blood and joints of arthritic patients.

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19 Syranyi, L., and Forro, E. Streptokokken im Blute mit besonderer Berücksichtigung der rheumatischen gelenkentzündung, Klin. Wchnschr. 7 453, 1928.

## THE PRESENT STUDY

Two years ago the present study was initiated in the Cornell Clinic by taking cultures from the tonsils and teeth of patients afflicted with chronic infectious arthritis. Later on the scope of the study was extended, and cultures were also taken from the blood and, when possible, from the joints. It is principally with the blood and joint cultures that the present report is concerned.

The type of patient in whom we have been particularly interested presents a rather characteristic clinical syndrome, namely, a chronic polyarthritis with swelling and often with some deformity and ankylosis of the joints affected. In order to delineate still more clearly the type of case studied, we submit the following composite picture.

The patient, usually of the neurotic type, gives a history of sudden or gradual development of pain, stiffness and swelling in several joints. He often dates the onset of his symptoms to some disturbance in his physical equilibrium, such as a trauma, an acute infection, exposure to cold or a surgical operation. Occasionally the onset of symptoms dates back to an attack of rheumatic fever. When the onset is sudden, the patient may run an irregular fever varying from 99 to 101 F, but when the onset is insidious, the temperature usually remains normal. The disease is almost always migratory in its early stages, jumping from joint to joint much as in rheumatic fever. After several attacks, however, the joints chiefly affected become permanently injured, and the process assumes a persistently chronic course.

The infection is prone to make its first appearance in the interphalangeal joints of the hands, frequently involving also the metacarpophalangeal joints of the fore and middle fingers. The joints gradually swell, with little or no pain, and in the course of time cause the fingers to assume the characteristic fusiform appearance. The knees are involved almost as frequently as the fingers. As the disease advances and involves other joints, the patient becomes uncomfortable. There is considerable disability, due to pain and stiffness on motion, and often there is persistent pain at night which interferes with the patient's sleep. The muscles become weak from disuse, and undergo atrophy. As a result, the patient's capacity for work and exercise is greatly diminished. Unless the disease is checked in its course, partial or complete ankylosis may occur in one or more joints.

On physical examination, the patient with chronic infectious arthritis presents a fairly typical picture. He is usually anemic, with a hemoglobin of seventy or under. If the condition is of long standing, the patient often appears chronically ill and undernourished, on the other hand, if it is an early case, the patient may be well nourished. The hands are cold and clammy and covered with perspiration. The swollen finger joints, which are characteristic, have on palpation a peculiar doughy or



rubber-like consistency, and in some instances the skin overlying the joint may become slightly bluish. The enlargement of the joint is due to the swelling and thickening of the synovial membrane and capsular ligaments. There is little if any pain on pressure, and only moderate pain on movement of the joint. In the larger joints, the signs of inflammation are more marked. There is more tenderness on pressure and more pain with movement. There may be an effusion of fluid in some of the larger joints. Of all the large joints, the knees are the most frequently affected. In a well established infection, the ankles, wrists, elbows and shoulders are usually implicated. The hip joints usually escape until late in the disease. The intervertebral joints are frequently involved, particularly in the cervical and lumbar regions. The temporomaxillary joints are frequently affected.

In the late stages of the disease, that is, after several years duration, more or less deformity and ankylosis develop, particularly in the hands and feet. Ulnar deviation of the fingers is a common occurrence.

Infectious arthritis runs a chronic course, extending over years. Usually, however, the progress is not continuous, periods of comparative comfort alternating with periods of active advance. With each attack there is a tendency for the joints to become progressively stiffer and more permanently injured.

Unless the disease is checked, the final stage is that of arthritis deformans. In the later stages, some of the periarticular swelling may disappear, due to the contraction of the fibrous tissue. In the joint itself, the granulation tissue becomes converted into adhesions which lead to immobilization. Late in the disease, bony changes also make their appearance. With loss of function, muscular atrophy becomes more and more pronounced. Many of these patients present a pitiful picture with their contracted, deformed limbs and marked wasting of the muscular tissue. Cardiac involvement is rare, even in advanced cases.

#### METHODS

1 *Blood Cultures*—The technic employed for blood cultures was an adaptation of that recommended by Clawson<sup>20</sup> in his blood culture studies of rheumatic fever.

Twenty cubic centimeters of blood was taken aseptically from the arm with a Luer syringe, placed in two sterile culture tubes and allowed to clot. Each tube was treated separately in the following way.

The tube was centrifugated, and all the serum drawn off with a sterile pipet. The clot was then broken up in the original culture tube with a sterile glass tube,  $\frac{1}{4}$  inch (6.35 mm) in diameter. The fragments of clot were drawn up in the same glass tube, and transferred to a 3 ounce bottle containing 50 cc of beef heart infusion broth with a  $p_H$  of 7.6 (0.5 per cent sodium chloride, 1 per cent peptone). The bottle was then put in the incubator at 37 C and left there unopened for five days.

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<sup>20</sup> Clawson, B. J. Studies on the Etiology of Acute Rheumatic Fever, *J Infect Dis* 36:444 (May) 1925.

At the end of this time, a tube containing 8 cc of a 15 per cent beef heart infusion agar was placed in the water bath and heated until the agar was completely melted. The tube was then partially cooled and 0.5 cc of whole rabbit blood added to it. Finally, the tube was seeded with 0.1 cc of broth from the original blood culture, and the contents poured into a petri dish. The culture was allowed to incubate for from twenty-four to forty-eight hours. Similar pour-plate cultures were made every three to five days thereafter until the original blood culture had been in incubation for thirty days. If, at the end of this time, the subcultures were still sterile, the sediment in the original blood culture bottle was drawn out with a sterile glass tube and centrifugated. After centrifugating, part of the sediment was examined by means of stained smears, while the remainder was cultured, part of it in fresh blood broth and part of it on blood agar plates. If these final cultures from the sediment showed no growth, the blood culture was considered sterile.

All of these cultures and transfers were made under a hood, in order to eliminate contaminations as far as possible. All contaminated cultures were discarded.

When colonies appeared on the plates, they were transferred into blood broth and identified by the usual bacteriologic methods.

*2 Joint Cultures*—Cultures from joints were made in blood broth from synovial fluid or synovial membrane, or from bony curettings removed from the joint at operation. When only tissue was available, the material was put in a bottle containing blood broth and macerated with a glass rod. These cultures, like the blood cultures, were incubated for several weeks and subcultured from time to time.

#### BLOOD CULTURES

One or more blood cultures were made from seventy-eight patients with chronic infectious arthritis (table 1). For the most part, the patients in this series presented the clinical picture already described, namely, pain and stiffness and usually swelling in several joints. In rare instances, only one joint was affected at the time the patient came under observation, but a careful history brought out the fact that other joints had previously been involved. In addition to pain, stiffness and swelling of the joints, most of the patients presented some deformity and ankylosis of the joints affected. Thirty-six of the seventy-eight patients showed one or more characteristic fusiform fingers. The ages of the patients varied from 7 to 74 years. Fifty-nine were under 50 years of age, while eighteen were 50 or over. The age of one patient was not obtained. The duration of the disease varied from one month to thirty-five years, but in a majority of the cases the disease had existed from one to three years at the time the patient came under observation. With a few exceptions, the patients were free from fever at the time cultures were taken.

In this group of seventy-eight patients, the blood cultures of forty-eight, or 61.5 per cent, were found, after varying periods of incubation, to contain a gram-positive micrococcus, growing either in pairs or in short chains. This micro-organism presented all the morphologic characteristics of a streptococcus (table 2). Some of the patients whose

TABLE 1—A Resume of Cases Studied with Results of Blood and Joint Cultures

History Number	Age	Sex	Duration of Arthritis	Probable Focus of Infection	Joints Affected*	Blood Culture†				Streptococcus Recovered	Strain Number	General Remarks
						1	2	3	4			
C 100	38	M	2 yr	?	T, V, K, A	—	+			T S	B 1	Synovial membrane from finger yielded no organism
C 101	28	M	2 yr	Tonsils	F, W, A, T	—	+	(—)		T S	B 2	
C 102	38	F	11 yr	Sinus	F, L, K	+				T S	B 3	
C 103	63	F	10 yr	?	F, W, A	+				T S	B 4	
C 104	33	F	2 yr	?	F, S	+				T S	B 5	
C 105	51	F	3 yr	Tonsils	F, A	+		(—)		T S	B 6	
C 106	10	F	1 yr	?	F, K, A	—	+			T S	B 7	Synovial membrane from finger yielded no organism
C 107	?	F	1 yr	?	F, W, V	+				T S	B 8	
C 108	60	F	3 yr	?	F, W, V	+	(—)			T S	B 9	
A 3592	33	F	1 yr	Colon	F, T	+	D	(—)		T S	B 10	
A 5237	26	F	5 yr	Tonsils	F, L, S, A	+				T S	B 11	
A 18019	58	F	1 yr	Tonsils	F, H	+				T S	B 12	
A 97225	35	F	5 yr	Tonsils	F, K	+	(—)			T S	B 13	
A 70252	30	F	4 yr	Tonsils	F, A, K	+				T S	B 14	
A 9320	7	F	8 mo	?	F, W, K	+	(—)			T S	B 15	
A 6750	11	F	1 yr	?	F	+				T S	B 16	
A 17177	57	M	5 yr	Tonsils	T, S	+				T S	B 17	Psoriasis
A 15311	58	F	1 yr	Colon	F, W, K	+		(—)		T S	B 18	
A 10347	38	F	2 yr	?	F, H	+				T S	B 19	Drythema nodosum
A 10110	62	F	5 yr	?	F, W	+				T S	B 20	
A 20132	27	F	1 yr	Tonsils	F, L, W, A	+				T S	B 21	
A 17088	50	F	2 yr	Tonsils	F, E, K	+	(—)			T S	B 22	
C 103	55	F	6 wk	Teeth	A, T	+				T S	B 23	
A 13920	52	F	2 yr	Tonsils	F, W	+	(—)			T S	B 24	
R-100	28	M	9 mo	Tonsils	F, S, K, A	+				T S	B 25	
A 11753	53	M	2 yr	Tonsils	F, A, K	+	—			T S	B 26	
N 100	71	F	15 yr	Tonsils	F, E, S	+	+			T S	B 27	
A 91103	23	F	5 yr	?	K, S	+	Z	+		T S	B 28	Erythema bullosum same organism recovered from bullae
R-103	41	F	2 yr	Tonsils	K, F	+				T S	B 29	
H 100	38	F	6 mo	?	F, S, H	+				T S	B 30	Ouretings from hip joint and pus from tooth yielded same organism
R 101	61	M	10 yr	Teeth	F, A, K	+		(+)	(—)	T S	B 31	
A 11301	49	M	2 yr	Tonsils	H, W	+				T S	B 32	
A 13013	26	F	6 wk	Tonsils	F, K, V	+	(—)			T S	B 33	
A 18061	53	M	5 yr	Tonsils	J	+				T S	B 34	Drythema nodosum
A 18668	30	M	2 yr	Tonsils	H, V	+				T S	B 35	
A 97227	51	F	5 mo	Intest	K	+				T S	B 36	Psoriasis
C 118	14	F	4 mo	?	F, W, K	+				T S	B 37	
R-106	35	M	?	?	F, A, H	+				T S	B 38	
A 92014	39	F	2 yr	Tonsils	F, K, S, F	+				T S	B 39	
		F			F, K, A	+				T S	B 40	
		F				+				T S	B 41	
		F				+				T S	B 42	
		F				+				T S	B 43	
		F				+				T S	B 44	
		F				+				T S	B 45	
		F				+				T S	B 46	
		F				+				T S	B 47	
		F				+				T S	B 48	
		F				+				T S	B 49	
		F				+				T S	B 50	
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		F				+				T S	B 64	
		F				+				T S	B 65	
		F				+				T S	B 66	
		F				+				T S	B 67	
		F				+				T S	B 68	
		F				+				T S	B 69	
		F				+				T S	B 70	
		F				+				T S	B 71	
		F				+				T S	B 72	
		F				+				T S	B 73	
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		F				+				T S	B 75	
		F				+				T S	B 76	
		F				+				T S	B 77	
		F				+				T S	B 78	
		F				+				T S	B 79	
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		F				+				T S	B 93	
		F				+				T S	B 94	
		F				+				T S	B 95	
		F				+				T S	B 96	
		F				+				T S	B 97	
		F				+				T S	B 98	
		F				+				T S	B 99	
		F				+				T S	B 100	



blood cultures yielded this organism on the first culture showed the same organism in the blood on the second or even third culture. In other patients one blood culture was positive while the second was sterile or vice versa, indicating that the micro-organism was not constantly present in the blood stream. Most of the cases were ambulatory. Comparatively few patients were confined to their beds. The impression prevailed that streptococci were more likely to appear in the blood stream during an exacerbation of joint symptoms.

The number of cases studied was too small to make any definite statement regarding the relationship between *Streptococcus bacteremia* and the duration of the disease, but there appeared to be a higher percentage of positive blood cultures in patients over 50 and in those who had had the disease for a number of years. One patient (A-94403) with a positive blood culture had had joint symptoms for only one

TABLE 2—Summary of Bacteriologic Observations in Blood Cultures of Patients with Chronic Infectious Arthritis

Type of Organism Found	Number of Cases
Typical strain (TS)	401
<i>Streptococcus viridans</i> (SV)	648
<i>Streptococcus nonhemolyticus</i> (SN-H)	21
<i>Diphtheroid bacillus</i> (D)	4
<i>Micrococcus zymogenes</i> (Z)	2

month. On the other hand, another patient (C-110) had been a sufferer from arthritis for thirty-five years. The following protocol is a good illustration of the type of patient on whom blood cultures have yielded streptococci.

A man (C-100), aged 38, came under observation on Jan 18, 1928. Following an attack of influenza two years previously, he began to have pain and stiffness in the fingers and shoulders. Within six months the pain had spread to practically every joint in the body and his ankles, knees and fingers had become swollen. When first seen, the chief symptoms were in the hands and feet, although occasional flare-ups occurred in other joints. The tonsils had been removed two years before, and several abscessed teeth had been extracted.

On physical examination, the patient was found to have several fusiform fingers on each hand (fig 1), a stiff neck, swollen ankles and feet and crepitation in the knees. Otherwise, the results of the physical examination were negative.

On January 19, a blood culture was taken. There was no growth after twenty-eight days of incubation.

On February 2, a second blood culture was taken. A streptococcus was recovered on the seventeenth day of incubation.

Clinically, this patient presented the typical picture of chronic infectious arthritis. The second blood culture yielded a streptococcus which on culture mediums resembled in some respects *Streptococcus viridans* and in others, *Streptococcus hemolyticus*.

*Other Bacteria Isolated From Blood Cultures*—Although some type of streptococcus has been by far the most frequent observation in our blood culture studies, other bacteria have occasionally been isolated. A diphtheroid bacillus was recovered from the blood cultures in four cases. In one of these (A-19685), a diphtheroid bacillus was isolated twice from the blood, and cultures from the cloudy fluid obtained from the knee joint yielded the same organism in pure culture. In another case (A-35972), the first blood culture showed a streptococcus, while the second revealed a diphtheroid bacillus in pure culture.



Fig 1—Typical fusiform fingers in patient C-100 with chronic infectious arthritis. A "typical strain" of streptococcus was isolated from the patient's blood.

In two cases of chronic infectious arthritis, *Micrococcus symogenes* was recovered from the blood. In one of these (A-7466), the first blood culture showed a streptococcus, the second culture *Micrococcus symogenes*, while the third culture yielded a streptococcus similar in all respects to the streptococcus first isolated.

*Staphylococcus albus* was occasionally isolated from the blood cultures, but in view of the frequent occurrence of this organism as a con-

tamnant in blood cultures, we have not been disposed to attach any significance to its presence

*Control Cultures*—It seemed important to check these observations in the blood of patients with chronic infectious arthritis by a series of blood cultures on patients with various other types of arthritis, on patients suffering from other infectious diseases, and on normal persons. Altogether, fifty-four controls were studied by means of blood cultures, the technic being similar in all respects to that used on patients with chronic infectious arthritis (table 3)

All the controls yielded sterile blood cultures. It is particularly interesting to note that seventeen cases of degenerative arthritis showed negative results. Four cases of gonococcal arthritis, three of chronic myositis and one of Still's disease showed no bacteremia.

TABLE 3—Classification of Patients Studied by Blood Culture

	Number of Cases Cultured	Total	Streptococcus in Blood Culture
Chronic infectious arthritis	78	78	48
Controls			
Degenerative arthritis	17	54	0
Gonococcal arthritis	4		
Rheumatic carditis	6		
Still's disease	1		
Chronic myositis	3		
Chronic neuritis	3		
Gout	1		
Chorea	2		
Tuberculous adenitis	2		
Diabetic neuritis	1		
Convalescent pneumonia	7		
Iridocyclitis	1		
Weak foot	1		
Normal persons	5		

#### JOINT CULTURES

In seven cases of chronic infectious arthritis, the opportunity presented itself for taking intra-vitam cultures directly from one of the involved joints (table 4). In six of the seven cases, synovial membrane or bony curettings were available, while in the seventh case cultures were taken from the synovial fluid of the knee joint. With two exceptions, all the cases fell definitely into the group of chronic infectious arthritis.

One exceptional case, D-100, was that of a child, 11 years of age, who developed a septic arthritis of the left hip during an attack of pneumonia. The hip joint was opened and drained. After the wound had healed the patient continued to have pain and stiffness in the hip. After three years of discomfort and partial ankylosis, a reconstruction operation was performed on the left hip joint, and at this time cultures were taken from small bits of bony curettings. *Streptococcus viridans* was recovered from the joint tissue, similar in all respects to that recovered from the blood.

The other exceptional case in this series, A-1936, was that of a man, 32 years of age, who had his knee injured in an automobile accident. Shortly afterward, stiffness and pain developed in the knee which had been subjected to trauma. No other joints ever became involved. Physical examination showed a swollen fluctuating knee with considerable atrophy of the muscles above and below the joint. An arthroplastic operation was performed, a piece of synovial membrane was removed and cultures were made. A nonhemolytic streptococcus was isolated from the culture. It is interesting to note that two blood cultures from this patient yielded in each case a pure culture of a diphtheroid bacillus.

In C-100 and C-107, both typical cases of chronic infectious arthritis with swollen joints and fusiform fingers, synovial membrane was removed from one of the fusiform finger joints and cultures were made. In both instances the cultures were negative for streptococci though both patients had shown streptococci in blood cultures. Perhaps the fact that the material in these two cases was rather scanty was responsible for the negative results obtained.

A woman (C-121), aged 37, had had pain and swelling of both knees for eight years. She also had pain in the left hip and lumbosacral region of four years'

TABLE 4—*Results of Cultures from Joints of Patients with Chronic Arthritis\**

No of Cases	Material Cultured	Organism Recovered from Joint	Organism Recovered from Blood
R-101	Curettings from hip joint	Streptococcus (T S)	Streptococcus (T S)
D-109	Curettings from hip joint	Streptococcus viridans	Streptococcus viridans
A-1936	Synovial membrane from knee joint	Streptococcus (S N-H)	Diphtheroid bacillus
A-1935	Synovial membrane and fluid from knee joint	Diphtheroid bacillus	Diphtheroid bacillus
C-107	Synovial membrane from fusiform finger joint	No growth	Streptococcus (T S)
C-100	Synovial membrane from fusiform finger joint	No growth	Streptococcus (T S)
C-121	Synovial fluid from knee joint	Streptococcus (T S)	No growth

\* T S = typical strain S N-H = Streptococcus nonhemolyticus

duration. For many years she had suffered from frequent sore throat. Physical examination showed swollen knees due to thickened synovial membrane and increase of synovial fluid. The remainder of her joints seemed free from disease at the time of examination. Fluid from the knee joint yielded a streptococcus. Two blood cultures were sterile.

A man (A-19685), aged 28, suffered from chronic infectious arthritis involving the toes, ankles, knees, spine and sacro-iliac joints of four years' duration. Physical examination showed a considerably swollen right knee, held in partial flexion. The right ankle was also swollen, with limited motion. The other joints showed no morbid changes. An arthroplastic operation was performed on the right knee, and cultures were taken from the synovial membrane and fluid. A diphtheroid bacillus was isolated in pure culture from the synovial membrane, and a blood culture was taken before the operation yielded the same organism.

A man (R-101), aged 61, presented the most interesting case in this series of patients subjected to joint cultures. He gave a history of pain and disability of both hips of ten years' duration. Physical examination showed that the left hip was ankylosed in a flexed position. The right hip had considerable limitation of motion, but was not ankylosed. A roentgenogram of the hip joints showed marked distortion and flattening of the head of the left femur, with obliteration of the interarticular space. The right side showed the same process but less advanced. The patient had one abscessed tooth, and following its extraction, he developed



pain and swelling of the left wrist. An arthroplastic operation was performed on the left hip, and cultures were made from some of the bony curettings. A streptococcus was recovered after thirteen days of incubation.

Cultures were made from the abscessed tooth and the patient's blood. From both sources there were cultivated streptococci, which were culturally and biologically identical with the organism recovered from the hip joint.

The organism isolated from the bony curettings of the hip joint was injected into a rabbit (table 8, rabbit 1). A chronic arthritis was produced, and at autopsy blood cultures from the rabbit yielded the same organism in pure culture.

Summarizing the seven cases of infectious arthritis in which cultures were obtained from arthritic joints, five of the seven yielded positive joint cultures. Four of the five positive cultures showed a streptococcus. Two of these streptococcal strains presented the appearance of hemolytic streptococci and were culturally similar to the type of streptococcus obtained in the majority of the blood cultures. The third strain was *Streptococcus viridans* and the fourth strain a nonhemolytic streptococcus. In one case, cultures from the joints yielded a pure growth of diphtheroid bacillus. It is significant that in four of the five cases with positive cultures from the joints, an organism identical in every way with the one isolated from the joint was also recovered from the blood.

#### CULTURAL AND BIOLOGIC CHARACTERISTICS OF THE STREPTOCOCCI ISOLATED FROM BLOOD AND JOINT CULTURES

On culture mediums, the streptococci which have been isolated from the blood and joints of patients with chronic infectious arthritis can be readily differentiated into three groups: (1) a streptococcus which presents the appearance of an attenuated *Streptococcus hemolyticus*, (2) *Streptococcus viridans*, (3) *Streptococcus nonhemolyticus*, or the so-called indifferent streptococcus. All of these streptococci have one feature in common, that is, their very slow growth in the original blood culture broth flasks. The average time of appearance of these streptococci as tested by frequent subcultures was approximately fifteen days. In some instances the flask had been in the incubator for thirty days before streptococci could be demonstrated. On the other hand, there were exceptional instances in which streptococci were isolated after four or five days of incubation. In a number of cases, when the original flask had shown no growth after thirty days of incubation, stained smears from the centrifugated sediment showed streptococci, and cultures taken from this sediment yielded streptococci.

In contrast to the original cultures, subcultures grew readily on the usual laboratory mediums. On blood agar plates, both superficial and deep colonies were usually recognizable after twenty-four hours of incubation. Subcultures in plain broth showed an abundant growth after twenty-four hours.

1 The type of streptococcus which has been encountered most frequently in the blood cultures is the organism designated as the "typical strain" It appears to be an attenuated *Streptococcus hemolyticus* In the forty-eight patients whose blood cultures yielded streptococci, forty, or 83.3 per cent, fell into this group Of the four strains of streptococcus isolated from arthritic joints, two fell into this group

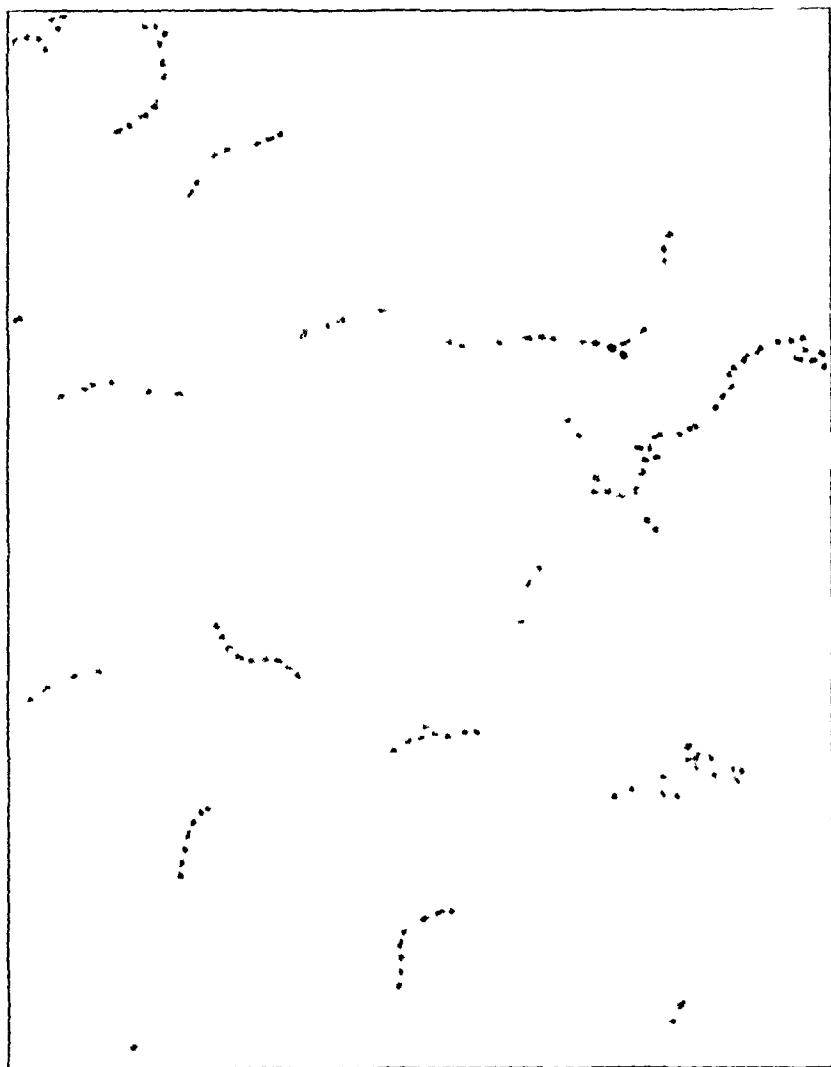


Fig 2—Smear from twenty-four hour broth culture of "typical strain" of streptococcus (no B-30) isolated from blood culture of patient R-101 Methylene blue stain, approximately  $\times 1000$

Morphologically, the "typical strain" is a very small gram-positive coccus, round or slightly oval, which in liquid mediums forms chains of from four to twenty cocci (fig 2) On solid mediums, the chains are shorter On blood agar plates, the colonies of this organism present a characteristic appearance After twenty-four hours' incubation, deep colonies appear as minute, biconvex, grayish colonies surrounded by a hazy zone of hemolysis The hemolytic zone is neither as clear nor as

wide as that of a typical *Streptococcus hemolyticus* colony (fig 3) Under the microscope, a small number of red blood cells can be seen throughout the hemolytic zone surrounding the colony There is also a small amount of methemoglobin formation visible

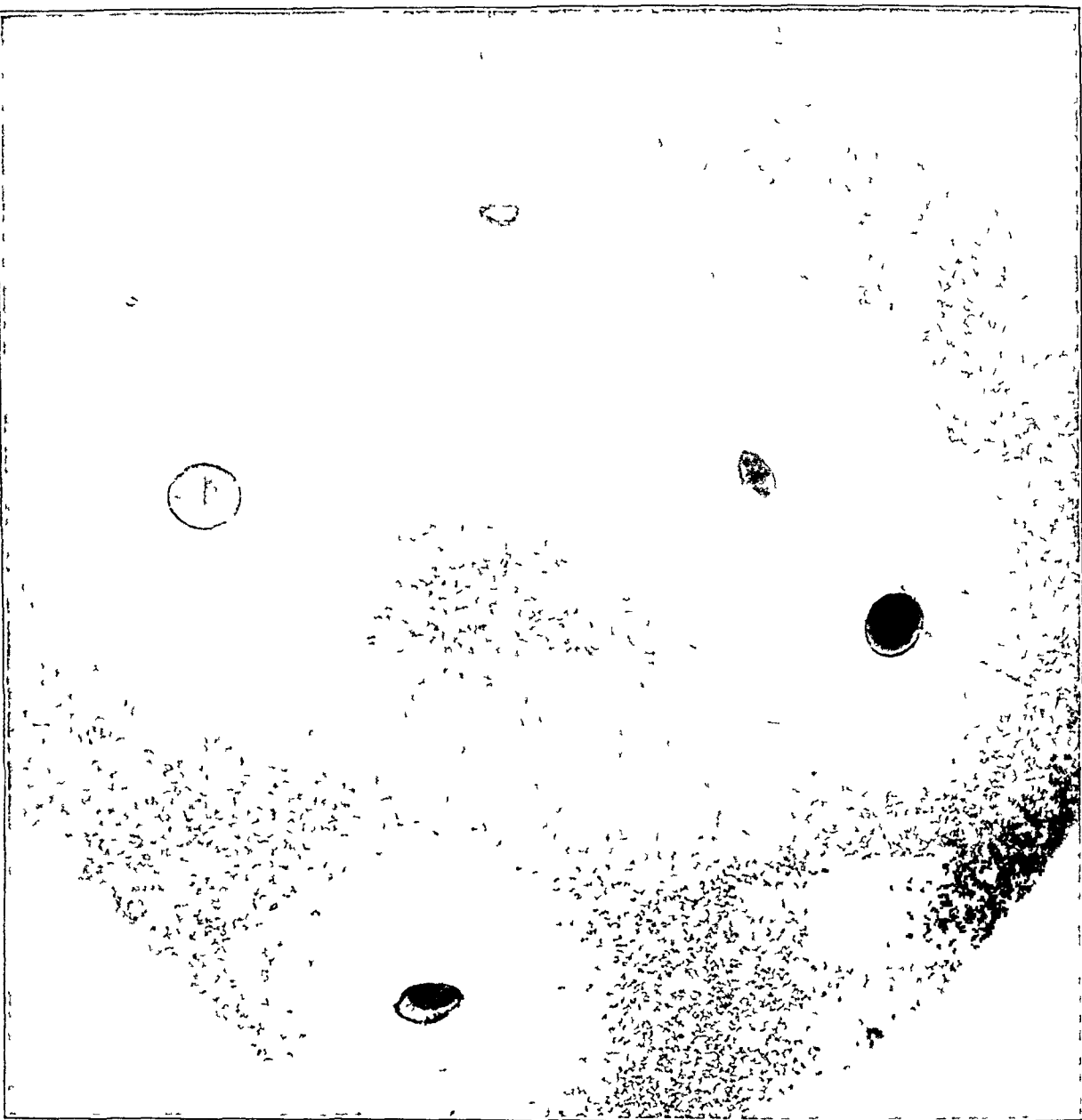


Fig 3—Deep colonies of “typical strain” of streptococcus number B-30 in a twenty-four hour blood-agar plate culture, approximately  $\times 40$

Superficial colonies on blood agar plates are round, gray, flatly convex, with dull rough surfaces By transmitted light, the superficial colony (fig 4) is also surrounded by some hemolysis, but the colony and the surrounding zone have a slight but definite greenish tinge The

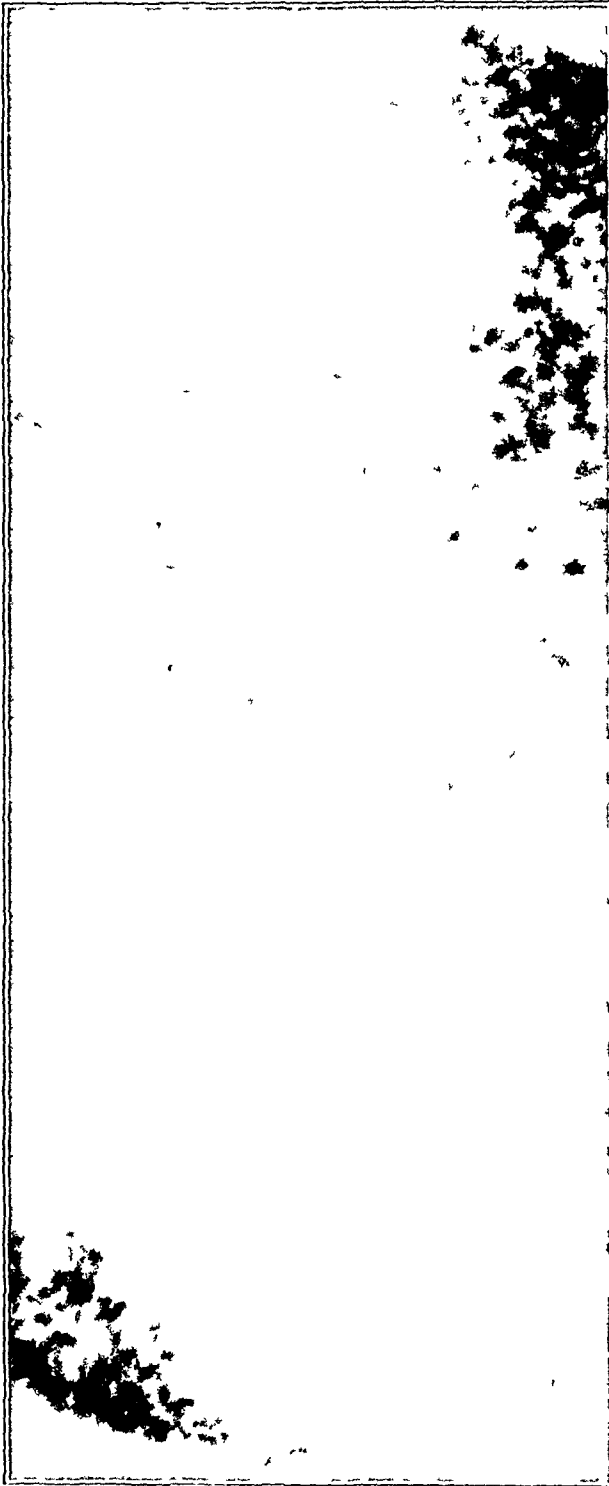


Fig 4—Superficial colonies of “typical strain” of streptococcus no B-30 in a twenty-four hour blood-agar plate culture, approximately  $\times 100$

superficial colonies are somewhat friable under the needle. When they are removed, the agar underneath is marked by a few specks of green pigment.

In blood broth, this organism grows readily with the production of a heavy granular and sometimes flocculent sediment, with slight turbidity of the medium. After twenty-four hours' incubation, a zone of hemolysis about 1 cm in depth appears at the bottom of the tube. Complete hemolysis of the blood cells never occurs during the first twenty-four hours of incubation, but may take place after several days of incubation. Blood broth cultures show little, if any, green discoloration. This organism grows readily in plain broth, producing a considerable amount of sediment, and throughout the medium a heavy granular growth which tends to adhere to the sides of the tube.

All the "typical strains" were insoluble in bile.

2 In a second but much smaller group of patients with chronic infectious arthritis, cultures from the blood and joints yielded a type of streptococcus which differed both culturally and biologically from the typical strain just described. Altogether, the blood cultures from six patients revealed a streptococcus which on blood agar plates produced colonies surrounded by zones of methemoglobin and which corresponded in all respects with the organism usually referred to as *Streptococcus viridans*. *Streptococcus viridans* was also recovered from one of the joint cultures.

Morphologically, these green streptococci resemble the "typical strain" in being small, but in liquid mediums they tend to grow in much longer chains. On blood agar plates the colonies present the usual characteristic appearance, small, gray, opaque colonies surrounded by a light greenish zone. In blood broth these streptococci produce a luxuriant growth which tends to settle to the bottom of the tube, leaving the supernatant fluid diffusely cloudy. The broth takes on a slightly greenish tinge, but there is no hemolysis. The growth in plain broth resembles that in blood broth.

3 In three patients an indifferent streptococcus which produced no change on blood agar plates was isolated. In cases A-19244 and R-105, this organism was recovered from the blood, while in the third patient (A-1936) the streptococcus was isolated in pure culture from the knee joint. Strangely enough, the blood culture from the latter patient showed no streptococci, but diphtheroid bacilli.

These strains of indifferent streptococci form small opaque red-brown colonies on blood agar, and resemble the streptococcus described by Small<sup>12</sup> and by Birkhaug<sup>21</sup> in their studies on the etiology of rheu-

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21 Birkhaug, K. E. Rheumatic Fever. Bacteriologic Studies of a Non-Methemoglobin-Forming Streptococcus with Special Reference to Its Soluble Toxin Production, J. Infect. Dis. 40: 549 (May) 1927.

matic fever This organism has been referred to by Small as *Streptococcus cardio-arthritidis* It should be noted that none of these three patients gave a history of rheumatic fever, nor did their arthritic manifestations resemble those of rheumatic fever

TABLE 5—*Fermentations Reactions and Solubility in Bile of Streptococcal Strains*

Typical Strains	May, 1928					Bile	November, 1928				
	Inulin	Man-nite	Dex-trose	Lac-tose	Sallein		Inulin	Man-nite	Dex-trose	Lac-tose	Sallein
B-1	—	—	+	+	+	—					
B-2	—	—	+	+	+	—	—	—	+	+	+
B-3	—	—	+	+	+	—	—	—	+	+	+
B-5	—	—	+	+	+	—	—	—	+	+	+
B-6	—	—	+	+	+	—	—	—	+	+	+
B-7							—	—	+	+	+
B-9							—	—	+	+	+
B-10	—	—	+	+	+	—	—	—	+	+	+
B-11	—	—	+	+	+	—	—	—	+	+	+
B-12	—	—	+	+	+	—	—	—	+	+	+
B-13	—	—	+	+	+	—	—	—	+	+	+
B-14							—	—	+	+	+
B-15	—	—	+	+	+	—	—	—	+	+	+
B-16							—	—	+	+	+
B-17							—	—	+	+	+
B-18	—	—	+	+	+	—	—	—	+	+	+
B-19	—	—	+	+	+	—	—	—	+	+	+
B-21	—	—	+	+	+	—	—	—	+	+	+
B-22	—	—	+	+	+	—	—	—	+	+	+
B-23	—	—	+	+	+	—	—	—	+	+	+
B-24	—	—	+	+	+	—	—	—	+	+	+
B-25	—	—	+	+	+	—	—	—	+	+	+
B-27	—	—	+	+	+	—	—	—	+	+	+
B-28							—	—	+	+	+
L-28	—					—	—	—	+	+	+
B-30	—					—	—	—	+	+	+
J-30	—	—	+	+	+	—	—	—	+	+	+
B-41	—	—	+	+	+	—	—	—	+	+	+
B-43	—	—	+	+	+	—	—	—	+	+	+
B-44	—	—	+	+	+	—	—	—	+	+	+
B-48							—	—	+	+	+
B-52							—	—	+	+	+
B-10	—	—	+	+	+	—	—	—	+	+	+
B-40'	—	—	+	+	+	—	—	—	+	+	+
B-53							—	—	+	+	+
J-46							—	+	+	+	+
Streptococcus viridans											
B-47	—	+	+	+	+	—	—	+	+	+	+
J-47	—		+	+	+	—	—	+	+	+	+
B-49						—	—	+	+	+	+
B-45						—	—	—	+	+	+
Streptococcus nonhemolyticus											
B-35	+	+	+	+	+	—	+	+	+	+	+
B-50						—	—	+	+	+	+
B-39						—	+	+	+	+	+

\* For the sugars, + indicates acid and clot, —, neither acid nor clot, for bile, — indicates no solubility

*Sugar Fermentations*—Sugar fermentations were carried out on thirty-six of the so-called "typical strains," on four of *Streptococcus viridans* strains, and on three of the indifferent strains Tests on five sugars were performed by two different methods at different times (table 5) In May, 1928, sugar-free broth was employed as a medium, while in November, Hiss' serum water medium was used In both cases, litmus was added as an indicator In both series, 0.1 cc of a

10 per cent solution of one of the sugars was added to each tube of culture medium. At the time of the test, 0.1 cc of a twenty-four hour sugar-free broth culture of streptococcus was added to each tube of sugar medium. The fermentation tubes were then allowed to incubate for seven days, and readings were made.

As will be seen in table 5, all of the "typical strains" with one exception acted uniformly on the sugars, fermenting dextrose, lactose and salicin, and having no effect on inulin and mannite. The exceptional strain (B-46) fermented inulin and mannite as well as the other sugars. This strain was isolated from the blood of a patient with high fever and a fulminating infection. This organism on culture mediums falls in the typical group, but according to the fermentation and agglutination tests, it is biologically independent. With this one exception, the sugar reactions for the typical strains were strikingly uniform. Furthermore, the reactions obtained in November were entirely consistent with those obtained six months earlier.

Four of the *Streptococcus viridans* strains were tested on the sugars (table 5). All of the four strains fermented dextrose, lactose and salicin. Three of the four fermented mannite. They had no effect on inulin.

The three strains of *Streptococcus nonhemolyticus* fermented mannite, dextrose, lactose and salicin. Two of the three fermented inulin.

*Agglutination Reactions*—In order to determine whether there was any biologic relationship between the streptococci which had been isolated from the blood and the joints of patients with chronic infectious arthritis, cross-agglutination tests were made with fifty strains (table 6). Rabbits were immunized against nine streptococci, seven of these being "typical strains" and the other two, *Streptococcus viridans*. The agglutination tests were carried out as follows:

A twenty-four hour broth culture of streptococcus was killed by heating the culture at 56 C for one hour. The sediment from 10 cc of the killed culture was then injected intravenously into a large rabbit. These injections of killed streptococci were repeated at five day intervals for six weeks. Ten days after the last injection, the rabbit was bled and the serum tested for agglutinins. If the rabbit serum did not show an agglutination titer of at least 1:1,280 against the homologous streptococcus, the rabbit was given further injections of killed organisms.

The antigens for the agglutination tests were prepared by growing the streptococci in potato broth for eighteen hours. By using this medium, a diffuse growth was obtained in the majority of cases. In the case of those strains that gave a granular growth in potato broth, a diffuse growth was obtained by transplanting the culture several times in plain broth before cultivating them in the potato broth. Before performing the tests the potato broth cultures were shaken vigorously for a minute or two, and then allowed to stand for a half hour. The upper portion of the culture was then removed for the agglutination test, 0.5 cc of the antigen was

mixed with 0.5 cc of the various dilutions of immune rabbit serum. The agglutinations were carried out to a titer of 1:1,280.

As controls, rabbit serum withdrawn before immunization was tested against the streptococci. Another control consisted of 0.5 cc of sterile broth and 0.5 cc of the culture. The agglutination tubes were left for two hours in the water bath.

TABLE 6—*Titer of Agglutination Reactions with Serums of Rabbits Immunized Against Seven "Typical" Streptococcus Strains and Two Streptococcus Viridans Strains*

Organisms	Serum T S B-2	Serum T S B-5	Serum T S B-6	Serum T S B-18	Serum T S B-22	Serum T S B-27	Serum T S E-28	Serum S V B-36	Serum S V B-47
T S * B-1	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	20
T S B-2	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T S B-2'	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	20
T S B-3	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	20
T S B-5	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	80
T S B-6	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	20
T S B-6'	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T S B-7	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	0
T S B-9	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	0
T S B-10	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T S B-11	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	20
T S B-12	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	0
T S B-12'	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	20
T S B-13	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	20
T S B-14	1,280	1,280	1,280	1,280	1,280	1,280	1,280	10	20
T S B-15	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T S B-16	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	20
T S B-17	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T S B-18	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	10
T S B-19	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T S B-21	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	10
T S B-22	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	0
T S B-23	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	0
T S B-24	1,280	1,280	1,280	1,280	1,280	1,280	1,280	80	0
T S B-25	1,280	1,280	1,280	1,280	1,280	1,280	1,280	10	0
T S B-27	1,280	1,280	1,280	1,280	1,280	1,280	1,280	80	20
T S B-28	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T S E-28	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T S T-28	80	160	160	160	160	80	10	10	0
T S B-30	1,280	1,280	1,280	1,280	1,280	1,280	1,280	10	0
T S J-30	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T S Tc-30	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	0
T S B-40	1,280	1,280	1,280	1,280	1,280	1,280	1,280	10	20
T S B-40'	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	20
T S B-40''	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	20
T S T-40	20	610	320	610	610	320	20	10	10
T S B-41	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	80
T S B-43	1,280	1,280	1,280	1,280	1,280	1,280	1,280	80	0
T S B-44	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	40
T S B-48	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	20
T S I-53							1,280		
T S B-32	80	80	80	80	80	80			80
T S B-46	0	0	0	0	0	0	0	0	0
S V B-47	20	20	10	10	80	20	20	20	1,280
S V I-47	20	40	20	80	80	10	20	80	1,280
S V B-36	20	80	10	80	10	40	0	1,280	610
S V B-45	20	80	20	80	80	40	20	160	20
S V B-49	10	80	160	160	160	40	10	320	160
S N-H B-35	0	0	0	0	0	0	0	0	0
S N-H B-50							0		
Controls									
S V	40	80	20	10	10	20	20	80	80
S H	0	0	0	0	0	0	0	0	0
S N-H	0	0	0	0	0	0	0	0	0

\* T S = "typical strain", S V = *Streptococcus viridans*, S N-H = *Streptococcus non hemolyticus*.

For the agglutination tests, the following dilutions of serums were used: 1:20, 1:40, 1:80, 1:160, 1:320, 1:640, 1:1,280. The figures in the table indicate the limit of agglutination with these dilutions; 0 = no agglutination.

The controls were stock cultures of streptococci obtained from sources other than arthritis. B = blood, J = joint, T = tonsil, Tc = teeth, I = erythema bullosa.



at 56 C They were then placed in the refrigerator and readings were made the following morning

Cross-agglutination tests were carried out with the nine immune serums, testing them against forty-three of the "typical strains" and seven of the atypical strains As will be seen in table 6, thirty-seven of the forty-three "typical strains" were agglutinated in dilutions as high as 1 1,280 by all seven of the serums of rabbits immunized against the "typical strain" One strain (B-32) agglutinated only to a dilution of 1 80 and one strain (B-46) did not agglutinate with any of the immune serums As pointed out under the fermentation tests, strain B-46 was isolated from the blood stream of a patient with septic arthritis This organism showed no biologic relationship to the other typical strains Two strains, T-28 and T-40, were isolated from excised tonsils and were agglutinated by the immune serums of typical strains as high as 1 160 and 1 640, respectively

One of the most interesting facts brought out by these agglutination reactions was the close biologic relationship between the "typical strains" isolated from the different foci in the same patient For example, B-28 was recovered from the blood stream, E-28 from an erythematous bulla and T-28 from the center of an excised tonsil of the same patient These three strains, culturally identical, were agglutinated by all the antiserums of the typical strains B-30 was isolated from the blood, J-30 from a joint and Te-30 from a root abscess in the same patient All three strains showed high agglutination with the antiserums of the typical strains of streptococci B-40 was isolated from the blood and T-40 from the tonsils of the same patient Both strains showed high agglutination with the antiserums of the typical strains When repeated blood cultures on the same patient showed streptococci, these streptococci were agglutinated equally well by the immune serums

In contrast to the high agglutinations with the serums of typical strains, the typical strains showed little or no agglutination with the two *Streptococcus viridans* serums Furthermore, *Streptococcus viridans* strains showed little or no agglutination with the serums of the seven typical strains They naturally gave high agglutination readings with the homologous *Streptococcus viridans* serums

The two strains of *Streptococcus nonhemolyticus* (B-35) and (B-50) showed little or no agglutination with either the serums of typical strains or the serums of *Streptococcus viridans* strains

In addition to these tests, the nine immune serums were tested against three control strains of streptococci The control *Streptococcus viridans* and the control *Streptococcus hemolyticus* strains had both been isolated from the sputum of patients who showed no symptoms of arthritis (*Streptococcus nonhemolyticus* was supplied to us by Dr James Small of Philadelphia) All of the immune serums produced a

slight agglutination of the control *Streptococcus viridans*, but had no effect whatever on either *Streptococcus hemolyticus* or *Streptococcus nonhemolyticus*

**Absorption Tests**—Absorption tests were carried out with three of the typical strain serums against fifteen of the typical strains and two *Streptococcus viridans* strains as follows

The sediment from 50 cc of a twenty-four hour broth culture of streptococcus was mixed with a 1:4 dilution of the immune serum. The mixture was shaken for three minutes and put in the water bath for two hours at 37 C. It was then allowed to stand in the icebox over night. In the morning, the mixture was centrifugated and the supernatant serum removed. Agglutination tests were set up in the same dilutions as those used in the original agglutination tests. Controls

TABLE 7—*Absorption Tests*

Degree of Agglutination of Streptococcal Strains with Serums from Three Immunized Rabbits before and after Absorption of Agglutinins

Antigen Typical Strains	Strain B-6			Strain B-2			Strain E-28		
	Absorbed Immune Serum	Unab- sorbed Immune Serum	Normal Serum	Absorbed Immune Serum	Unab- sorbed Immune Serum	Normal Serum	Absorbed Immune Serum	Unab- sorbed Immune Serum	Normal Serum
B-6	0	1,280	0	0	1,280	0	0	1,280	0
P-2	0	1,280	0	0	1,280	0	0	1,280	0
I-28	0	1,280	0	0	1,280	0	0	1,280	0
B-22	0	1,280	0	20	1,280	0	0	1,280	0
B-15	0	1,280	0	0	1,280	0	0	1,280	0
B-3	0	1,280	0	0	1,280	0	0	1,280	0
B-13	0	1,280	0	0	1,280	0	20	1,280	0
B-9	0	1,280	0	0	1,280	0	0	1,280	0
B-39	0	1,280	0	0	1,280	0	0	1,280	0
B-24	0	1,280	0	0	1,280	0	0	1,280	0
B-17	0	1,280	0	0	1,280	0	0	1,280	0
B-25	0	1,280	0	0	1,280	0	20	1,280	0
B-27	0	1,280	0	0	1,280	0	0	1,280	0
B-14	0	1,280	0	0	1,280	0	0	1,280	0
B-11	0	1,280	0	0	1,280	0	20	1,280	0
Strep vir strains									
B-49				40	40	0			0
B-47	40	40	0	40	40	0			

In the absorption tests, the following dilutions of serums were used for the agglutination reactions: 1:20, 1:40, 1:80, 1:160, 1:320, 1:640, 1:1,280. The figures in the table indicate the limit of agglutination with these dilutions, 0 = no agglutination.

were carried out with unabsorbed serum and normal rabbit serum. All the tubes were put in the water bath at 56 C for two hours, then in the icebox over night. Readings were made on the following morning.

As will be seen in table 7, there was almost complete absorption by all the fifteen typical strains. In tests for *Streptococcus viridans*, the readings were the same as before the absorption tests were performed.

#### RELATION OF STREPTOCOCCI RECOVERED FROM THE BLOOD TO STREPTOCOCCI ISOLATED FROM JOINTS AND FROM FOCI OF INFECTION

An interesting phase of this investigation has been the correlation of the streptococci isolated from the blood with streptococci cultivated from the joints and from various foci of infection. Several cases will now be cited.

A man (A-11301), aged 49, had pain and stiffness in the feet, knees, right elbow, shoulders and back of two years' duration. The results of physical examination of the joints were essentially negative. The tonsils were moderately enlarged and infected. Cultures were made from the patient's blood on three different occasions, and each time a streptococcus of the typical strain was isolated in pure culture. All three strains were biologically identical. A streptococcus recovered from the excised tonsils was culturally similar to the streptococcus isolated from the blood, and it was agglutinated by serums of "typical strains" in dilution as high as 1:640 (table 5, B-40, B-40', B-40" T-40).

A woman (A-94403), aged 23, gave a history of pain and swelling of the knees and fingers, of one month's duration. Physical examination revealed an early case of chronic infectious arthritis with beginning fusiform fingers. Both knees were slightly swollen and tender. The patient had numerous erythematous bullae on both legs. The tonsils were small, cryptic and diseased. Cultures were made from the patient's blood, from the excised tonsils and from fluid aspirated from the bullae. From each source a streptococcus of the "typical strain" was isolated, and all three strains were morphologically and culturally identical (table 6, B-28, E-28 T-28). The streptococcus isolated from the tonsils was agglutinated by serums of "typical strains" as high as 1:160. The streptococcus isolated from the bullae was agglutinated by the serums of typical strains as high as 1:1,280.

In case R-101 (complete protocol in section on joint cultures) there were "typical strains" of streptococcus in cultures from the blood, from the hip joints and from a root abscess. The streptococci from all three sources were agglutinated by serums of typical strains as high as 1:1,280 (table 6, B-30, J-30, Te-30).

These three protocols furnish evidence that in patients with chronic infectious arthritis, foci of infection may harbor a streptococcus culturally and biologically identical with the strain of streptococcus isolated from the blood or joint. Comparatively little attention has been devoted to this phase of our problem, but we hope to investigate it more thoroughly in the future.

#### EXPERIMENTAL ARTHRITIS

Several of the strains of streptococcus which have been isolated from the blood and joints of patients with chronic infectious arthritis have been injected into various laboratory animals with the idea of determining the virulence of these organisms and also their capacity to produce an experimental arthritis. The typical strains differ somewhat in their virulence for mice, some killing a mouse in doses of 0.5 cc of broth culture, while others produced little or no effect. The typical strain is fairly virulent for rabbits, 5 cc of broth culture intravenously usually kills the animal in forty-eight hours. On the other hand, doses as large as 10 cc intravenously produce no symptoms in a ringtail or a rhesus monkey.

*Experimental Arthritis*—Eleven rabbits were given intravenous injections of streptococci which had been isolated from the blood of patients with arthritis (table 8). Ten of these received some one of the typical strains, and the eleventh received *Streptococcus viridans*. Of

TABLE 8—*Resumé of Rabbit Experiments*

Number of Rabbit	Weight, Gm	Strain of Streptococcus Injected	No of Injections Before Arthritis Appeared	Total Number of Injections	Joints Affected	Duration of Arthritis	Loss of Weight, Gm	Blood Culture*	Joint Culture	Lesions in Heart	Remarks
1	2,800	B-30	8	10	Interphalangeal, elbows	2 mo	910	Strept T S	—	None	
2	3,880	I-28	17	18	Knees, left elbow, shoulders	3 mo	630	Strept T S	—	None	Died of pneumonia
3	1,250	B-27	1	4	Interphalangeal, elbows	1 wk	260	Strept T S	Strept T S	None	
4	1,550	J-17	1	23	Left wrist, left elbow	6 wk	170	Negative	Negative	—	Animal gradually recovered
5	2,100	B-5	1	6	Wrists, right elbow	6 wk	80	—	Strept T S	None	
6	1,275	B-2	6	12	Right elbow, right wrist	2 mo	70	Strept T S	Strept T S	None	
7	950	B-12		1	None	—	—	—	—	None	Died 24 hours after injection
8	1,720	B-21	2	3	Interphalangeal, left knee, right elbow	3 wk	120	Strept T S	Strept T S	None	
10	1,120	B-36		5	None	—	10	—	—	None	Died 3 weeks after last injection
12	2,500	B-46		4	None	—	500	—	—	None	Died 2 weeks after last injection
27	1,950	B-40		1	None	—	—	—	—	None	Died 24 hours after injection

\* Strept T S = typical strain of streptococcus

the eleven rabbits, seven developed arthritis in one or more joints, while the remaining four failed to show symptoms (table 8)

The usual mode of procedure was as follows

A broth culture of streptococcus was centrifugated and the sediment resuspended to the original concentration in saline. The initial dose was from 0.5 to 1 cc intravenously. Injections were repeated at intervals of from three to five days, the dose being increased each time. The maximum dose was 5 cc. In none of the rabbits were symptoms noted after the first or second injections. Symptoms in the joints usually appeared after the fifth or sixth injection, in one rabbit, however, arthritis did not appear until after the seventeenth injection.

The only abnormal signs noted in the affected rabbits were limping and loss of weight. On examination, the affected joints were swollen and tender. Various joints were involved. Because of the frequent involvement of the interphalangeal joints of man, it was particularly interesting to note the frequent involvement of the interphalangeal joints of the rabbits. One or both elbows were involved in all seven cases, the knees in two cases and the wrist in two cases. The shoulder joint was involved only once.

Six of the seven rabbits eventually died after running a course of from two and one half to nine months. The remaining rabbit recovered completely from the disease in spite of repeated injections of streptococci.

At autopsy, all the rabbits were found to have lost considerable weight. The affected joints were swollen, and, when the joints were opened a slightly cloudy mucoid fluid presented itself. The periarticular tissues appeared thicker than normal, and the synovial membrane was congested. The internal organs appeared normal. The condition of the heart was noted particularly with regard to vegetative endocarditis. No vegetations were observed in any of the rabbits.

Bacteriologic study of these arthritic rabbits resulted in observations similar to those obtained in the human patient. Blood cultures were taken of six of the affected rabbits, and in five of the six animals a streptococcus morphologically and culturally identical with the organism injected was recovered from the blood. The blood cultures were taken from five to thirty days after the last intravenous injection of streptococci. One rabbit (no. 2) showed a positive blood culture thirty days after the last intravenous injection. The organism did not appear in the blood culture flasks until after ten days of incubation.

In five of the seven rabbits with arthritis, fluid from one of the affected joints was cultured and a streptococcus morphologically and culturally identical with the organism injected was recovered from the synovial fluid in four cases.

Microscopic sections through the affected joints presented a variable picture, depending on the duration of the arthritis. In cases of only a few weeks' duration, the interarticular space contains mucus and broken-down cells and sometimes a considerable number of leukocytes. There may be some superficial necrosis of the cartilage, and the synovial membrane is thickened and infiltrated with leukocytes and plasma cells. Many large endothelial cells are noticed. Rabbits in which the arthritis has existed for several months show changes of a more chronic nature. There is less exudate in the joint cavity, and the synovial membrane takes on the appearance of chronic granulation tissue, the deeper part being composed of newly formed connective tissue, and the superficial part rich in cellular elements. The leukocytes are mostly lymphoid and plasma cells, together with a large number of macrophages, which appear to be undergoing transition into fibroblasts.

Summarizing the pathologic changes in these joints, it may be said that in the experimental arthritis produced by the typical human strain of streptococcus, the histologic sections show a gradual transition from a stage of fairly acute inflammation to a subacute or chronic condition with considerable new formation of fibrous tissue.

When sections from one of the affected joints of a rabbit with chronic arthritis (fig 5) are compared with sections from a fusiform finger in man (fig 6), a striking similarity is seen in the two pictures. Indeed, without some method of identification, it would be impossible to tell which section came from the rabbit and which from the human lesion.

The following protocols illustrate the pathologic changes in a rabbit with experimental arthritis and in a patient with chronic infectious arthritis.

A belgian hare, rabbit 1, weighing 2,265 Gm, was injected intravenously twice weekly (Nov 24, 1927, to March 1, 1928) with broth cultures of a "typical strain" of streptococcus isolated from the bony curettings of the patient in case R-101 (see protocol under joint cultures). The dose of culture ranged from 0.5 to 2 cc. The animal gradually lost weight, and on Jan 23, 1928, the first symptoms of arthritis were noted in the knees. They were slightly swollen, and the animal limped. On February 22, the elbows became swollen, the right more than the left. The condition of the knees gradually cleared up, and at the time of death on March 30, they did not show any swelling.

At autopsy, the elbows were both distinctly swollen, but there was no definite evidence of arthritis in any other joint. The internal organs were entirely negative. The heart showed no pathologic changes. Blood taken from the heart shortly before the death of the animal gave a positive culture of a typical strain of streptococcus identical with the one injected. The joint culture was negative.

Microscopic sections through one of the elbows showed the following changes (fig 5). The synovial membrane was considerably thickened and presented the appearance of chronic inflammatory tissue. The endothelial lining had been almost completely replaced by a thin layer of necrotic tissue, which at some points contained numerous leukocytes, mostly of the lymphoid type. Beneath the layer of



Fig 5—Microscopic section of synovial membrane from elbow of rabbit 1 with experimental arthritis produced by “typical strain” of streptococcus B-30, hematoxylin-eosin stain, reduced from an approximate magnification of  $\times 140$



Fig 6—Microscopic section of synovial membrane from a fusiform finger of patient C-107. Note the superficial necrosis and dense infiltration of leukocytes near the right margin. Hematoxylin-eosin stain, reduced from an approximate magnification of  $\times 140$

necrosis, there was a thick zone of loose connective tissue infiltrated at many points with leukocytes and plasma cells. The leukocytes were mostly of the lymphoid type, although polymorphonuclear leukocytes were also present. Plasma cells were abundant. Areas of hyaline degeneration occurred at some points in the connective tissue.

A woman (C-107), aged 32, came in with a history of pain and swelling of the joints of four years' duration. Symptoms first developed in the fourth toe of the right foot. Shortly after this, symptoms appeared in the spine and fingers. The elbows and wrists recently became involved. Physical examination showed several fusiform fingers and swelling of both wrists. Each of two blood cultures yielded the "typical strain" of streptococcus. Cultures were taken from a piece of synovial membrane removed from one of the fusiform fingers, but no organisms were recovered.

Microscopic section through the synovial membrane showed a vascular and rather loose connective tissue, infiltrated with lymphoid and plasma cells and a moderate number of polymorphonuclear leukocytes. The endothelial lining in some places was normal. At other points the endothelial cells were piled up and stratified. At still another point the tissue showed extensive necrosis and over this area the epithelium had been entirely destroyed and its place taken by a layer of polymorphonuclear leukocytes. In the deeper parts, the tissue showed areas of hyaline degeneration. The section presented the typical picture of chronic granulation tissue.

Figure 5 is a photomicrograph of a section from the elbow of rabbit 1, and figure 6 a photomicrograph of a section from the synovial membrane in case C-107. The similarity of the tissue changes in the two sections is striking.

#### COMMENT

In the early part of this article we have shown what confusion has existed in the minds of investigators concerning the etiology of chronic arthritis. Furthermore, we have pointed out that even among bacteriologists who have at times obtained positive cultures from the blood or from the joints of arthritic patients, there has been marked discrepancy in the results obtained. It was because of this confusion and doubt as to the etiology of the disease that the present study was undertaken.

Altogether, seventy-eight patients with chronic infectious arthritis have been subjected to blood cultures. Of these seventy-eight cases, forty-eight, or 61.5 per cent, yielded a streptococcus. Of the forty-eight strains of streptococcus isolated from blood cultures, forty, or 83.3 per cent, were found to be culturally and biologically identical and presented the appearance of attenuated hemolytic streptococci. Of the eight remaining strains, six were classified as *Streptococcus viridans*, two as *Streptococcus nonhemolyticus*. In this report the predominant strain has, for lack of a better name, been referred to as the "typical strain." In the earlier part of our work, we were disposed to look on this dominant organism as an atypical *Streptococcus viridans* because of its capacity to produce some green coloration on blood agar plates.



However, after several generations on artificial mediums, the typical strains all showed definite hemolytic properties, not so marked as typical *Streptococcus pyogenes*, but sufficient to produce a zone of hemolysis on blood agar plates and considerable reddening in blood broth. Furthermore, the reactions of the "typical strains" on sugars were consistent and corresponded to those of the beta type of streptococcus. Our hesitancy in classifying this organism was not dispelled when we sought the opinion of several bacteriologists. One called it streptococcus alpha prime (a subvariety of *Streptococcus viridans*), two considered it *Streptococcus hemolyticus*, while a fourth was unwilling to express a positive opinion. Dr. J. Howard Brown, who has had a large experience with streptococci, wrote

In spite of the slight evidence of methemoglobin formation, I think I would regard these streptococci as of the beta type because there is no real zone of methemoglobinized corpuscles next to the streptococcus colonies. This is also substantiated by the fact that serum broth cultures produce complete hemolysis of washed rabbits' cells in less than two hours.

We are very much disposed to accept Dr. Brown's opinion and call this 'typical strain' *Streptococcus hemolyticus*. However, in view of the divergence of opinions, it seems wiser to suspend final judgment until the organism has received further study and to refer to it for the present as the "typical strain."

The fact that in our experience 83 per cent of the streptococci isolated from the blood of patients with chronic infectious arthritis have fallen into one biologic group, strongly supports the theory that a considerable proportion of all cases of chronic infectious arthritis are caused by a biologically specific strain of streptococcus. The comparatively small remainder of cases appears to be referable to either *Streptococcus viridans* or *Streptococcus nonhemolyticus*. It should not be forgotten that rarely a clinical syndrome indistinguishable from chronic deforming arthritis can be produced by the gonococcus.

Our investigations into the bacteriology of the joints in chronic infectious arthritis have not been as extensive as the blood cultures, but the isolation of streptococci from a number of joints would indicate that the joint lesions in this disease are actual infections. The interesting theories propounded by Swift,<sup>22</sup> and more recently by Zinsser,<sup>23</sup> as to the allergic nature of the joint lesions in rheumatic fever may or may not be applicable to chronic infectious arthritis. The latter disease appears

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22 Swift, H. F., Derick, C. L., and Hitchcock, C. H. Rheumatic Fever as a Manifestation of Hypersensitiveness (Allergy or Hyperergy) to Streptococci, *Tr. A. Am. Phys.* **43**: 192, 1928.

23 Zinsser, H., and Yu, H. The Bacteriology of Rheumatic Fever and the Allergic Hypothesis, *Arch. Int. Med.* **42**: 301 (Aug.) 1928.

to have its perfect analogue in gonococcal arthritis, an infectious disease in which a primary gonococcal focus of infection in the prostate or seminal vesicles produces lesions in the joints by metastatic infection through the blood stream

In the small series of joint cultures studied, the results were consistent with those obtained from blood cultures. The "typical strain" of streptococcus was isolated from the joint in two cases, *Streptococcus viridans* in one case and a nonhemolytic streptococcus in one. In two of the four cases with positive joint cultures, a streptococcus identical with the one isolated from the joint was also recovered from the blood.

To our minds, one of the most significant features of this study has been the correlation of streptococci isolated from a focus of infection with streptococci recovered from the blood or from the joints of the same patient. In several instances, the identity of these streptococci has been clearly proved by the similarity of their cultural and biologic reactions.

Our studies on experimental arthritis in animals are still in the preliminary stage. Several interesting facts have already been brought out. It is comparatively easy to produce a chronic nonsuppurative arthritis in rabbits with the "typical strain" of streptococcus. In rabbits with experimental arthritis, the "typical strains" can be recovered from the blood and from the infected joints. Finally, the histologic changes which take place in the joint of a rabbit with experimental arthritis are strikingly similar to those which occur in the joint of a patient with chronic infectious arthritis. When, in a patient with typical chronic infectious polyarthritis, a biologically specific strain of streptococcus has been isolated from the tonsils, from the blood stream and from one of the infected joints, when this streptococcus isolated from the patient produces similar lesions in the joints of rabbits, and when the same organism is recovered from the blood stream and from the affected joints of the rabbit, it is hard to avoid the presumption that this streptococcus is the cause of the disease.

A diphtheroid bacillus was recovered from the blood in four patients with chronic infectious arthritis, and in one of the four a diphtheroid was removed from an infected joint. This organism has been isolated by other bacteriologists from the blood and joints of arthritic patients. We are not disposed to attach much significance to its presence. Diphtheroids have been found so frequently in lymph glands of both healthy and diseased patients that their occasional presence in the blood or even in the joint would not be surprising.

*Micrococcus zymogenes* was isolated from the blood of two patients with chronic infectious arthritis. We are not prepared to express an opinion as to the etiologic significance of this organism at the present time.

A considerable number of the patients in this series have been treated with autogenous or stock streptococcus vaccines. In many cases the results have been encouraging, furthermore, in a number of instances, inoculations with vaccine appear to have sterilized the blood stream. Sufficient time, however, has not yet elapsed to permit of a final judgment as to the therapeutic value of vaccine.

Perhaps a few suggestions should be offered to any who may undertake a study of the bacteriology of the blood and joints in chronic infectious arthritis. The following points are all essential for successful results.

1. Select the proper type of patient. Patients with polyarthritis with swelling of several joints, preferably with one or more fusiform fingers, give the highest proportion of positive blood cultures.

2. Take plenty of blood, from 20 to 30 cc., for the blood culture.

3. Take several blood cultures on each patient, preferably after the joints have had some exercise.

4. A  $p_H$  of 7.6 is the optimum for the blood cultures.

5. The original cultures must be kept under observation in the incubator for at least four weeks, subcultures being taken every four or five days during this period. Before finally discarding the original broth flasks, some of the medium should be centrifugated and cultures and smears made from the sediment.

If, as appears highly probable from this study, chronic infectious arthritis is usually a streptococcus infection, what shall be said of the etiology of hypertrophic or degenerative arthritis? For some time there has been a growing conviction among many students of arthritis that degenerative arthritis is not a truly inflammatory process and that it is noninfectious in nature. Such a conception of degenerative arthritis is supported by the results of this study. All the blood cultures taken from patients with degenerative arthritis were sterile. Unfortunately, no opportunity for taking joint cultures on these patients presented itself. At the present time all the evidence at hand points to the conclusion that degenerative arthritis is just one more phase of the somatic deterioration which we call old age.

Some writers on arthritis have attempted to make a distinction between chronic infectious arthritis and arthritis deformans. The presence of streptococci in the blood and joints of both these clinical types would seem to indicate that there is no basis for such a distinction. Certainly from our own studies we are forced to conclude that arthritis deformans is nothing more than the end-result of chronic infectious arthritis. The "deformans" type usually presents a history of long standing.

## CONCLUSIONS

1 A streptococcus can frequently be isolated from the circulating blood of patients with chronic infectious arthritis (61.5 per cent in this series of seventy-eight cases)

2 Of these streptococci, 83.3 per cent are culturally and biologically identical, and appear to be attenuated hemolytic streptococci. This dominant strain has been referred to as the "typical strain." The remaining strains fall definitely into either the viridans or the indifferent group of streptococci.

3 A streptococcus, culturally and biologically identical with the strain isolated from the blood, can sometimes be cultivated from one of the affected joints in the same patient.

4 A streptococcus, culturally and biologically identical with the strain isolated from the blood and joints, can sometimes be isolated from a focus of infection in the same patient.

5 When the "typical strain" of streptococcus is injected intravenously into rabbits, a majority of the rabbits develop a chronic non-suppurative polyarthritis. Microscopically, the histologic changes in the rabbit's joints are practically identical with those observed in the joints of patients with chronic infectious arthritis.

6 Cultures from the blood and from the joints of rabbits infected with experimental arthritis frequently yield a streptococcus identical with the strain originally injected.

7 These observations tend strongly to confirm the theory that chronic infectious arthritis is a streptococcal infection, caused in a large proportion of cases by a biologically specific strain of this organism. The presence of this specific strain of streptococcus in the blood of several patients with advanced arthritis deformans goes far to corroborate the view already widely held that arthritis deformans and chronic infectious arthritis are one and the same disease.

# CLINICAL SIGNIFICANCE OF PREMATURE BEATS

WITH PARTICULAR REFERENCE TO HEART RATE \*

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The relationship that premature beats bear to prognosis is a question that has called forth many and varied opinions. There are, on the one hand, those who have considered them to be entirely benign and, on the other hand, those who have thought them evidence, in every case, of underlying cardiac disease. Between these two extremes their clinical moment is appraised in various gradations of severity. Long before the advent of the modern methods of studying arrhythmia and the recognition of the several different types of this condition, it was recognized by some that premature beats, or pulse intermittence as they were then termed, were not always to be interpreted in a serious light. There is still so much uncertainty about the significance of premature beats under varying conditions that new information based on more than impressions is highly desirable. Such information regarding the significance of premature beats at varying heart rates is herewith recorded.

## LITERATURE

Although the earliest medical literature in Greek and Roman times mentioned intermittence of the pulse rate, there was not a clear separation between its significance and that of the other types of arrhythmia. In general, Galen regarded irregularity of the pulse rate as a bad sign, and all through the Middle Ages Galen's views held sway.

Heberden,<sup>1</sup> however, writing in 1782, said, "Some books speak of intermitting pulses as dangerous signs, but I think without reason, for such trivial causes will occasion them that they are not worth regarding in any illness unless found with other bad signs of more moment." In 1884, Richardson<sup>2</sup> quoted from an article he had written in 1868, in which he said that although he could not find an author who had made a special study of intermittency, he himself believed that, "In

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<sup>1</sup> From the Cardiac Clinic and Laboratory of the Massachusetts General Hospital

1 Heberden, W. Commentaries on History and Cure of Diseases, London, 1782

2 Richardson, B W. Intermittency of the Heart and Circulation, Aesclepiad, London, 1 193, 1884

itself, when it is not present to an exaggerated degree, (it) is often less dangerous than it seems" He based this opinion on its common occurrence after middle age and on the long duration of life of many who present intermittency He mentioned one patient who died at the age of 86 and was first known to have had an irregular pulse rate at 42 Interestingly too, he noted that alcohol quickens the pulse and causes the intermittency to disappear, which is later followed by a slowing at which time it is more pronounced He mentioned also that he had, in the treatment of intermittency, sometimes combined quinine with opium with marked benefit

Several other cases have been recorded in which premature beats have been present for many years Thus, Mackenzie<sup>3</sup> cited the case of a man in whom he noted auricular premature beats at the age of 69 They were first discovered when the patient was 18, at which time he was rejected for an appointment to India on account of the irregularity During many of the intervening years he had been forced to earn his livelihood by work that entailed great bodily strain, and had been much depressed at times by the grave prognostications of his medical advisers, who led him to believe that his end might come at any moment He was in fairly good health when seen by Mackenzie after fifty-one years with premature beats Grassmann<sup>4</sup> reported a case in which they were known to be present for sixty-seven years, Koppang<sup>5</sup> one of thirty years' duration, Walsh<sup>6</sup> one of forty years', and Shultze<sup>7</sup> quoted the observation of Erb who noticed them in himself at the age of 29 They continued and for twenty-seven years he had no impairment of health After this for seven years he had attacks of tachycardia, but these did not disturb his work or mountain climbing At 73 he survived a grave operation on the gallbladder and died at the age of 83 from infectious enteritis Allan<sup>8</sup> and Brown,<sup>9</sup> among others, likewise wrote that premature beats are compatible with long life

Some authors have looked on premature beats as being largely due to the effects of the nervous system Kaufmann and Rothberger<sup>10</sup>

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3 Mackenzie, James Diseases of the Heart, London, Oxford University Press, 1913

4 Grassmann, Karl Zur prognostischen Wertigkeit und Behandlung der praktisch-wichtigsten Herzarrhythmien, München med Wchnschr **67** 5, 1920

5 Koppang, N Ueber Extrasystolie, Ztschr f arztl Fortbild **21** 63, 1924

6 Walsh, J J Prognosis in Functional Heart Disease The Story of Forty Years of Premature Systole, Internat Clin **4** 158, 1926

7 Schultze, F Zur Frage der praktischen Bedeutung und der Behandlung der Extrasystolie, Deutsche med Wchnschr **50** 1357, 1924

8 Allan, G A Defects in Cardiac Rhythm in Relation to Cardiac Failure, Glasgow M J **95** 333, 1921

9 Brown, W L The Irregular Heart, Med Rev **16** 1, 1913

10 Kaufmann, R, and Rothberger, C J Ueber Extrasystolische Pulsarrhythmien, Wien klin Wchnschr **33** 599, 1920

stated that they are almost always dependent on extracardiac nerve stimulation, particularly vagal Cautley<sup>11</sup> said they are not a cardiac but a nervous symptom, Hoffmann<sup>12</sup> thought that they may arise from pure nervous and psychic causes as well as from high blood pressure Many have regarded premature beats as being of little, if any, significance in themselves and have expressed the belief that the prognosis in any case must be based on the accompanying or underlying cardiac conditions<sup>13</sup> Similarly, Bass,<sup>14</sup> writing of premature beats in childhood, stated that premature beats of toxic origin including those which occur in rheumatic fever are not necessarily a symptom of permanent injury

Lewis<sup>15</sup> has been a little more guarded in his views He believed that although premature beats in themselves cannot be regarded as evidences of serious involvement of the heart muscle, still they constitute and bear witness to defects, and single ones may be the precursors of grave conditions Grassmann<sup>4</sup> was of the opinion that long observation of the case is necessary for prognosis, and Babcock<sup>16</sup> believed that in the course of time they have harmful effects Reilly<sup>17</sup> stated that

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11 Cautley, Edmund Irregularity of the Heart, *St Barth Hosp Rep* **29** 283, 1893

12 Hoffmann, A Ueber die Entstehung der Extrasystolen Irregularität, *Munchen med Wchnschr* **53** 1987, 1906

13 Mackenzie, J Some Manifestations of the Healthy Heart in the Young Frequently Taken as Indications for Treatment, *Brit M J* **2** 1697, 1912 Lohman, W H The Diagnosis, Prognosis and Treatment of Common Disturbances of Cardiac Rhythm, *Long Island M J* **9** 361, 1915 Griffith, T W Discussion on Cardiac Irregularities Especially in Reference to Prognosis and Treatment, *Brit M J* **2** 697, 1924 Grewe, J E Premature Ventricular Systoles Their Clinical Significance, *J A M A* **67** 1072 (Oct 7) 1916 Price, F W Recent Advances in the Diagnosis, Treatment and Prognosis of Heart Disease, *Brit M J* **1** 477, 1913 Maldague, L L'extrasystolie, *Rev med de Louvain* **25** 289, 1909 Leyden, E The Prognosis of Diseases of the Heart, *Woods Med & Surg Monograph* **5** 57, 1890 Wenckebach, K Arrhythmia of the Heart, London, W Green and Son, 1904 Galli, G Contributo al Significato Pronostico delle Extrasystole Cardiache, *Policlinico* **25** (sez prat) 1256, 1918 Smith, A L Clinical Study of One Hundred Patients with Extrasystoles as Seen in Office Practice, *Ann Clin Med* **3** 385, 1924 Mackenzie (footnote 3)

14 Bass, M H Significance of Cardiac Extrasystoles in Childhood, *J A M A* **86** 387 (Feb 6) 1926

15 Lewis, T Clinical Disorders of the Heart Beat, London, Shaw & Sons, 1913

16 Babcock, R H Prognosis in Cardiac Affections, as Related to the Discovery of Murmurs and to Arrhythmia, *J A M A* **70** 355 (Feb 9) 1918

17 Reilly, T F The Problem of the Irregular Heart, *Internat Clin* **4** 62, 1915

their presence in organic heart disease increases the seriousness of the prognosis by 10 per cent Vaquez,<sup>18</sup> Leconte<sup>19</sup> and Ritchie<sup>20</sup> looked on ventricular as less serious than auricular and nodal premature beats, and further considered their onset in hypertensive cases as the precursor or first sign of cardiac involvement

Satterthwaite<sup>21</sup> considered premature beats in high temperatures as indicative of severe toxemia, in convalescence, of a weak heart, in pneumonia or rheumatic fever, as suggesting cardiac complications Hewlett<sup>22</sup> quoted Mackenzie as saying that they are particularly ominous when they occur at the height of infectious fevers Strickland-Goodall,<sup>23</sup> Smith<sup>24</sup> and Hirschfelder<sup>25</sup> emphasized the point that in a patient in whom premature beats are developed or increased by exercise, the prognosis is more serious Nefedoff<sup>26</sup> looked on their presence in heart disease as enhancing the seriousness of the prognosis and he also believed them dangerous with high blood pressure, because cerebral hemorrhage may follow the large postextrasystolic beat Roth<sup>27</sup> stated that nervous influences increase, but that it is doubtful if they can ever induce premature beats in an otherwise healthy organ He mentioned focal infections as a cause of them and believed it more likely that the nervous influence merely augments the disturbance in a heart that is already the seat of some pathologic process or one that bears the brunt of at least a mild toxemia Mortensen,<sup>28</sup> in speaking of premature beats, concluded that even though such causes as tobacco, tea and coffee are a factor in producing them, nevertheless, in the great majority of cases there is underlying cardiac disease, and all of the cases in which

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18 Vaquez, H Prognostic et traitement des arrhythmies, Arch d mal du coeur 4 3, 1911

19 Leconte, M L'extrasystole, Paris, J B Bailliere et fils, 1911

20 Ritchie, W T Prognosis in Certain Affections of the Heart, Lancet 2 643, 1920

21 Satterthwaite, T E Newer Conception of Cardiac Arrhythmias and Treatment, M Rec 75 833, 1909

22 Hewlett, A W Common Cardiac Arrhythmias and Their Clinical Significance, Internat Clin 4 47, 1907

23 Strickland-Goodall, J The Premature Contraction and Its Significance, New York M J 115 204, 1922

24 Smith, F M The Premature Contraction, Wisconsin M J 20 114, 1921-1922

25 Hirschfelder, A D Diseases of the Heart and Aorta, Philadelphia, J B Lippincott Company, 1918

26 Nefedoff, V Frequence, origine et signification des phenomenes extrasystoliques au coeurs des cardiopathies, Arch d mal du coeur 6 711, 1913

27 Roth, I R Cardiac Arrhythmias, New York, Paul B Hoeber, 1928

28 Mortensen, M A Diagnosis and Management of Extrasystolic Type of Cardiac Irregularities, Lancet-Clinic 113 353, 1915



they appear must be looked on as potentially pathologic. Muller<sup>29</sup> voiced the most pessimistic opinion of all, affirming that, "There is no doubt extrasystoles in the majority of cases are due to incipient or advanced diseases of the myocardium. If a great number of extrasystoles disturb the normal pulse rate, we are always sure of a severe damage to the heart muscle. It is better in practice to consider them as signs of importance and not simply as the manifestation of a nervous heart which commonly passes as harmless."

Koppang<sup>5</sup> reported the results of 1,000 tracings taken in 62 cases following diphtheria. Forty-two of these patients had serious cardiac complications. In seventeen tracings he found premature contractions. They were present in the same frequency at varying rates and appeared from the tenth to the sixtieth day of convalescence, with two exceptions which occurred in patients with other cardiac complications. He concluded that premature contractions are a symptom of myocardial involvement following diphtheria in contrast to those encountered in routine practice. He also found them in 7 per cent of 200 cases of hypertension, but doubted if they were caused by high blood pressure. He had seen them frequently in patients with low blood pressure, and had also noted in cases of hypertension that they could be produced by psychic influences.

#### PRESENT STUDY

The lack of definite data as to the significance of premature beats at varying heart rates and the variable opinions expressed caused us to make the study herein reported. Are cases in which premature beats occur at the more rapid rates more serious than those in which they occur at the slower rates?

Our series is composed of 200 patients, 100 of whom showed premature beats and 100 normal rhythm. None of them evidenced a marked degree of auriculoventricular or intra-ventricular block. They were all seen and electrocardiograms were made at the Massachusetts General Hospital, between the years 1915 and 1926, and all have been followed to the present time. The clinical diagnoses in the cases of the two groups were similar. We have divided each group of 100 into four subgroups of 25 each, one with heart rates less than 80, one with rates between 80 and 100, one with rates between 100 and 120 and one with rates over 120.

Of the 100 patients who presented premature beats, 56 were males and 44 females. When they were grouped in the several decades according to their age at the time of examination, it was found that 5 were in the first decade, 9 in the second, 5 in the third, 10 in the fourth, 21 in

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<sup>29</sup> Muller, F. Nervous Affections of the Heart, Arch Int Med **11** (Jan) 1908

the fifth, 27 in the sixth, 15 in the seventh, 7 in the eighth and 1 in the ninth. The incidence of cardiac disease, of disease elsewhere in the body and of the apparently healthy is shown in the accompanying table, in which our figures are compared with similar ones of Lewis and Pardee<sup>30</sup>

The higher incidence among the healthy in our series may be due to the inclusion of more cases seen in private practice. Undoubtedly premature beats among healthy persons at large are relatively much more frequent than the figures in the table indicate, as these series were, for the most part, collected from hospital cases.

The number of patients with premature beats who died in the different heart rate groups, together with the number of patients used as control cases who are dead, in each group, is shown graphically in chart 1. It will be seen that there is practically no increase in the death rate of the premature beat series until the heart rate of 120 is reached, and beyond that rate there is only a moderate increase. The

*Incidence of Cardiac Disease, Disease Elsewhere in the Body and the Apparently Healthy*

	Heart Disease, per Cent	Disease Elsewhere, per Cent	Healthy, per Cent
Lewis	71	19	10
Pardee	81	10	6
Present series	63	22	15

rather marked increase in the deaths of those of the control group with heart rates of from 100 to 120 we believe should probably be attributed to an insufficient number of cases in the series, as the clinical diagnoses in this group correspond closely to the diagnoses in the premature beat group. This inconsistency can be corrected partially by dividing each series into two groups, one with heart rates less than 100 and one with rates over 100. The graphic representation of the number of deaths when the two series are thus divided is shown in chart 2. It is seen then that the number of deaths in the two series correspond closely, and those cases in the premature beat series show a mortality at faster heart rates that is no higher than those of the control series with no premature beats. In other words, as the basic heart rate increases so does the mortality increase but no faster in those patients with premature beats than in those without premature beats.

Barker<sup>31</sup> reported a series of 193 patients with premature beats divided into one group of 76 who had no other signs of heart disease

<sup>30</sup> Pardee, H. E. B. *Clinical Aspects of the Electrocardiogram*, New York, Paul B. Hoeber, 1928.

<sup>31</sup> Barker, P. S. Significance of Extrasystoles, *Ann Clin Med* 2:371, 1923-1924.

and a second group of 117 patients with premature beats with other signs of heart disease. In the former group the known dead with auricular premature beats amounted to 22.5 per cent, with ventricular premature beats, 17 per cent. In the latter the known dead among the auricular group was 51 per cent, among the ventricular, 27 per cent. Rearranging his cases we find that these two groups taken together

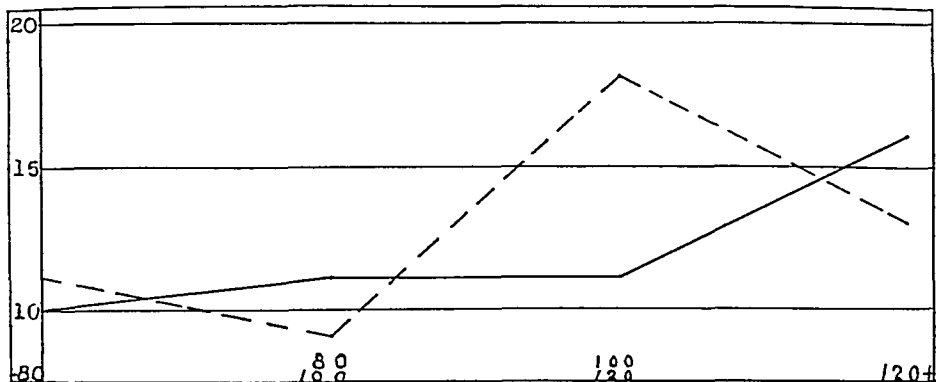


Chart 1—The number of patients with premature beats who died, and the number of patients used as controls who died. The abscissae represent the number of patients dead, the ordinates the heart rates. The cases of premature beats are shown by the heavy line and the control cases by the broken line.

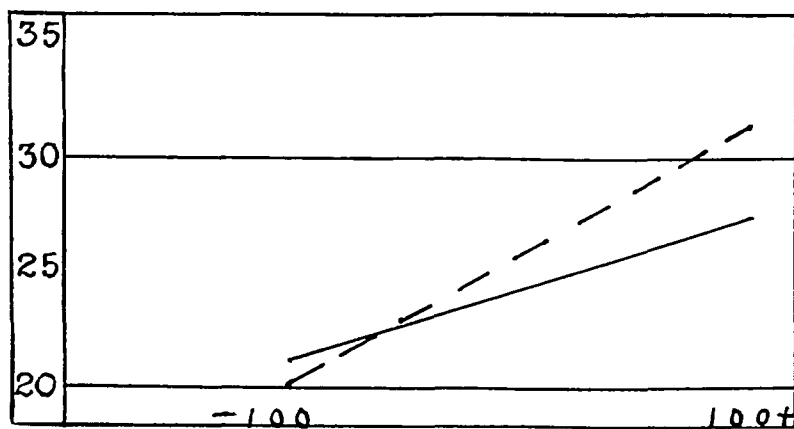


Chart 2—The number of deaths in the series in which the heart rates were less than 100, and those in the series in which the heart rates were more than 100. The abscissae represent the number of patients dead, the ordinates the heart rates. The cases of premature beats are shown by the heavy line, and the control cases by the broken line.

show a total mortality for auricular premature beats of 36 per cent and a total mortality for ventricular premature beats of 27 per cent. In our series, we have followed all the cases and consequently have a higher mortality in both types, however, we find that the comparative

number of deaths among those of the auricular type (thirty-seven cases) and those of the ventricular type (sixty-three cases) is the same, the ventricular being slightly in excess. Our percentages show 45 per cent of the patients with auricular and 50 per cent of the patients with ventricular premature beat to be dead within a period of thirteen years.

In our group of cases we have 63 with ventricular premature beats. Of these 55 were unifocal in origin and 8 were of multifocal origin. D'Irsay<sup>32</sup> studied 100 cases of premature beats, presumably ventricular, to determine the relative significance of those arising from multiple foci as compared with those arising from a single focus. He concluded that diseases representing pathologic change in the myocardium show a higher percentage of ventricular premature beats from multiple foci than from one focus. Forty-one of our patients with ventricular premature beats showed evidence of heart disease. Of these, 34, or 83 per cent, were unifocal and 7, or 17 per cent, were multifocal in origin. D'Irsay also stated that diseases not involving the heart are not accompanied by multifocal premature beats. In one of our cases multifocal premature beats were recorded without clinical or electrocardiographic evidence of any other abnormalities in the heart or elsewhere. This patient is living and well four years after the original electrocardiogram was taken. Furthermore, d'Irsay stated that the multifocal type gives a much more grave prognosis than the unifocal. In our series, among the patients who showed multifocal premature beats the mortality is 63 per cent as compared with 46 per cent mortality among those of the unifocal group. Many more cases must be studied before definite conclusions can be reached as to how much more serious multifocal extrasystoles may be than unifocal extrasystoles.

#### SUMMARY

1 A series of 100 cases of premature beats, divided into four heart rate groups, and followed over a period of years, is presented. This is accompanied by a series of a similar size of control cases, having the same diagnoses as those of the premature beat group but not showing arrhythmia.

2 Premature beats which occurred at the more rapid rates in this series did not bear a more serious prognosis than those at slower rates when allowance was made for the increase in mortality due to increased rate alone.

3 The presence of premature beats in the series reported here added no gravity to the prognosis. The death rate was actually slightly greater in the 100 cases with normal rhythm.

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32 d'Irsay, S. On the Meaning of Extrasystoles, *Am J M Sc* **174** 96, 1927

4 Auricular premature beats were not found to be more significant so far as prognosis of life is concerned than were ventricular premature beats

5 Multifocal ventricular premature beats did not appear to bear a much more serious prognosis than those of unifocal origin, neither were they present in our patients who showed evidence of heart disease to nearly the degree of those of the unifocal type It is doubtful if multifocal premature beats are always accompanied by myocardial involvement

6 The frequency with which premature beats occurred in a given case seemed to bear little relation to prognosis <sup>33</sup>

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33 In our experience, the rare exceptions in which premature beats occur more often than once every other beat, tend to have auricular fibrillation or ventricular paroxysmal tachycardia and serious heart disease Only four such cases, however, have been observed at the Massachusetts General Hospital in thirteen years in more than 5,000 cases in which electrocardiography was done Also, it may be added that some years ago one of us reported a higher death rate in patients with auricular fibrillation when there was a complication of ectopic ventricular contractions (White, P D Prognosis in Heart Disease in Relation to Auricular Fibrillation and Alternation of the Pulse, *Am J M Sc* **157** 5, 1919)

# CHLORIDE METABOLISM AND ALKALOSIS IN ALKALI TREATMENT OF PEPTIC ULCER \*

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Only within the last three years has the literature definitely suggested the important relation of chloride metabolism to alkalosis in the Sippy <sup>1</sup> alkali treatment for peptic ulcer. Hardt and Rivers <sup>2</sup> were probably the first to suggest that the symptomatology of alkalosis might be partly due to the reduction of blood chlorides, however, the chlorides were normal in the one case they examined. Work has been done on upper intestinal and pyloric obstruction <sup>3</sup> and on salt-poor <sup>4</sup> and salt-free <sup>5</sup> diets, but I have found no articles which compare the observations and symptoms of these conditions with the strikingly similar pictures found in alkalosis from Sippy treatment.

A study of the material in this paper and a comparison with the observations of others will show the paramount importance of chloride metabolism in the treatment for ulcers. I hope that a clearer understanding of the complications of Sippy therapy will result from studies such as these and help to quiet the dissatisfaction revealed in the literature. The objections of Smithies <sup>6</sup> are characteristic, however, the rapid symptomatic relief, the high percentage (about 85 per cent) of conditions cleared up symptomatically and roentgenologically, and even the rapid clearing of partial pyloric obstruction <sup>1</sup> from spasm and edema are results not readily obtained with other methods of therapy.

## SIGNS AND SYMPTOMS AND RESULTS OF LABORATORY EXAMINATION IN ALKALOSIS

With a clear picture of the alkalosis from alkali therapy in mind, one can make comparisons with the alkalosis of chloride depletion and of chloride privation. Then one can see more clearly the relationship and importance of chloride metabolism to alkali treatment.

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\* From the Medical Division of the Research Laboratories and the Department of Gastro-Enterology of the Henry Ford Hospital, Detroit

1 Sippy, B W. Gastric and Duodenal Ulcer, J A M A **64** 1625 (May 15) 1915, *ibid* **79** 26 (July 1) 1922

2 Hardt, L L, and Rivers, A B. Toxic Effects of Alkali Treatment, Arch Int Med **31** 171 (Feb) 1923

3 Haden, R L, and Orr, T G. Acute Symptoms Following Gastro-enterostomy, Bull Johns Hopkins Hosp **34** 26, 1923, Blood Changes After Intestinal Obstruction, Surg Gynec Obst **37** 465, 1923. MacCallum et al. Pyloric Obstruction in Relation to Gastric Tetany, Bull Johns Hopkins Hosp **31** 1, 1920

4 Austin, J H, and Jonas, L. Effect of Diet on Chloride Excretion in the Dog, J Biol Chem **33** 91, 1918. Mayer (footnote 24)

5 Frown, A. Chlorides and Gastric Secretion, Presse méd **30** 1096, 1922

6 Smithies, Frank. Non-Surgical Management of Peptic Ulcer, J A M A **85** 674 (Aug 29) 1925

Symptoms ascribed to alkalosis by various writers are lassitude, irritability, dizziness, distaste for food, nausea and vomiting, aching in the muscles and joints, slow respirations, increased pulse rate,<sup>2</sup> dry throat, dry and itching skin,<sup>7</sup> mental dulness and stupor, dull headaches and even muscular twitchings and tetany<sup>8</sup>

In one case I observed a marked craving for salt, and in cases of chronic alkalosis, marked weakness, especially in the legs, fatiguability, dyspnea on exertion and cramps in the legs. A few patients have shown absolute intolerance to neutralizing doses of alkali, one patient developed marked nausea and vomiting even though there was considerable free acid in the gastric contents. Another patient developed diarrhea, apparently due to the soda in the powders.

In some cases, Hardt and Rivers<sup>2</sup> and Venables<sup>9</sup> reported evidence of disturbed kidney function with profound toxic symptoms and even death. Albumin, pus, erythrocytes and casts were found in the urine, the blood urea and plasma carbon dioxide capacity were increased, and the phenolsulphonphthalein output of the kidneys was depressed. MacCallum<sup>10</sup> has shown that the depletion of chlorides by vomiting and aspiration produces symptoms of alkalosis, nerve irritability and tetany in dogs. In addition, Hastings, Murray and Murray<sup>11</sup> noted a rise of carbon dioxide capacity. Frouin<sup>5</sup> noted lassitude, dulness, muscular twitching and weakness, paresis of the posterior extremities and convulsions with fits of anger in dogs kept on salt-free diets. Achlorhydria occurred on the eighth day, and after three weeks diminished secretion in the stomach, diminished absorption in the intestine and a diminution of all the mineral salts obtained. He said that Bischoff found a diminished excretion of urea. Houghton<sup>12</sup> and Haden and Orr<sup>13</sup> observed lassitude, dulness, evidence of uremia, tetany, etc., in the hypochloremia of pyloric and upper intestinal obstruction.

The carbon dioxide capacity of the plasma<sup>14</sup> has been used considerably as a measure of alkalosis. Kast, Myers and Schmitz<sup>15</sup> indi-

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7 Jordan, S. M. Calcium, Chlorides and Carbon Dioxide Content of Blood in Alkali Treatment, *J. A. M. A.* **87** 1906 (Dec 4) 1926.

8 Grant, S. B. Tetany. Report of Cases with Acid-Base Disturbance, *Arch. Int. Med.* **30** 355 (Sept.) 1922.

9 Venables, J. F. Alkalosis Following Alkali Treatment, *Guy's Hosp. Rep.* **75** 152, 1925.

10 MacCallum (footnote 3, third reference).

11 Hastings, A. B., Murray, C. D., and Murray, H. A. Changes in Blood After Pyloric Obstruction, *J. Biol. Chem.* **46** 223 1921.

12 Houghton, L. W. Toxemia Following Pyloric Obstruction, *Guy's Hosp. Rep.* **75** 149, 1925.

13 Haden and Orr (footnote 3, first and second references).

14 Van Slyke, D. D. Determination of Carbonates and Carbon Dioxide in Solutions, *J. Biol. Chem.* **30** 347, 1917.

15 Kast, L., Myers, V. C., and Schmitz, H. W. Alkalosis, *J. A. M. A.* **82** 1858 (June 7) 1924.

cated that the  $p_H$  as well as the carbon dioxide content should be taken to get a true picture of the acid-base balance. The carbon dioxide content is said to give more information than the capacity, because, according to van Slyke,<sup>16</sup> the  $p_H$  is a function of the ratio of basic carbonates to carbonic acid ( $\text{BHCO}_3$  :  $\text{H}_2\text{CO}_3$  ratio), an increase in the ratio increasing the  $p_H$ , the carbon dioxide content is the sum of carbon dioxide as carbonic acid and carbonates. In the average case of alkalosis from alkali therapy, however, there is little consistent difference. Myers and Gatewood<sup>17</sup> found this to be true.

Myers and Booher<sup>18</sup> and van Slyke<sup>19</sup> showed that the carbon dioxide capacity or content is not necessarily increased in alkalosis, and, on the other hand, increased carbon dioxide capacity does not always indicate true alkalosis, as the  $p_H$  may be normal. A  $p_H$  above 7.47 indicates a true uncompensated alkalosis. Unfortunately, I could make few  $p_H$  determinations simultaneously with the determinations of the carbon dioxide content and capacity.

#### OTHER EFFECTS OF ALKALI

After a course of alkali therapy, Friedenwald<sup>20</sup> found in 44 per cent of his cases an increased free and total acid, in 22 per cent a diminished secretion and the rest were irregularly affected. Lockwood and Chamberlin<sup>21</sup> gave alkali with the test meal. There was a temporary neutralization, but afterward a tendency for the acid secretion to rise above normal in 50 per cent of the patients given sodium bicarbonate, in 25 per cent of those given calcium carbonate and in 20 per cent of those given magnesium oxide. The temporary neutralizing effects of the last two alkalis were more prolonged.

I obtained the gastric response from day to day while the patient was on alkali therapy, but in the two cases studied longest, large frequent aspirations on account of partial pyloric obstruction depleted the chloride reserve. Low chloride reserve diminishes acid secretion.<sup>5</sup> Therefore, these results are inconclusive as to the effect of alkalis per se on gastric secretion.

The observations of Friedenwald and of Lockwood and Chamberlin have formed the basis of one of the strong objections to alkali therapy.

16 Van Slyke, D. D. Studies in Acidosis. *J. Biol. Chem.* **30** 289, 1917.

17 Myers and Gatewood. Acid-Base Balance in the Blood of Peptic Ulcer Cases Treated with Alkalies, Paper at the annual meeting of the American Gastro-Enterological Association, Atlantic City, N. J. May 2, 1927.

18 Myers, V. C., and Booher, L. E. Variations in Acid-Base Balance of the Blood in Disease, *J. Biol. Chem.* **59** 699, 1924.

19 Van Slyke, D. D. Variations of Acid-Base Balance of the Blood, *J. Biol. Chem.* **48** 153, 1921.

20 Friedenwald, J., Gantt, W. H., and Morrison, T. H. Studies in Fractional Analysis, *Ann. Clin. Med.* **2** 292, 1924.

21 Lockwood, A. L., and Chamberlin, H. G. Effects of Alkali on Gastric Secretion and Motility, *Arch. Int. Med.* **32** 74 (July) 1923.



however, an increase of acid secretion, which is likely a temporary affair, will not be a serious drawback if the neutralization of free acid is obtained without producing other complications. I have not found studies definitely indicating more frequent recurrence of ulcer after treatment with alkali.

In the blood of patients under alkali treatment, Sara M. Jordan<sup>7</sup> found some increase of calcium, depression of chlorides, most marked in the first few days and then settling to a level, and elevation of carbon dioxide content. In addition, Myers and Gatewood<sup>17</sup> studied the  $p_{\text{H}}$ , the nitrogenous products and other constituents of the blood which might play a part in producing symptoms of alkalosis.

I have followed the general chloride metabolism as closely as possible to determine the rôle played by variations in the chloride balance. A test meal of 50 cc. of 1 per cent cooked corn starch, containing 1 cc. of 0.5 per cent phenolphthalein and neutralized until barely pink with tenth normal sulphuric acid, was introduced into the stomach while fasting, through a Rehfuess tube after complete aspiration. After half an hour the gastric contents were withdrawn and a sample of oxalated blood was obtained. The blood was kept from contact with air by the use of liquid petrolatum.

#### REPORT OF CASES

As an introduction to the discussion, excerpts from a few random case histories will be given and some partial observations tabulated.

*Acute Hypochloremia with Normal Carbon Dioxide Capacity*—CASE 1—E. G., a white man aged 26, had a condition that was diagnosed duodenal ulcer and irritable colon. The urine showed a faint trace of albumin with sulphosalicylic acid. The blood showed nonprotein nitrogen, 31.3 mg. per hundred cubic centimeters (normal from 25 to 35). The kidney function was 50 per cent phenol-sulphonphthalein output in two hours (normal from about 50 to 70 per cent). Sippy treatment was started on March 8, 1926, with 55 soda units (40 grams [2.6 Gm.] of powder containing three parts soda and one part calcium carbonate). On March 10, the aspirations were acid. On March 11, the milk "tasted bad," nausea and a dull feeling in the head developed and the patient craved something salty. To date, the aspirations totaled 315 cc., representing about 1.5 Gm. of sodium chloride. (For convenience, all chlorides are expressed as sodium chloride.) The whole blood chlorides were 410 mg. per hundred cubic centimeters (normal about 450), and the plasma chlorides were 500 (normal about 570). The carbon dioxide capacity of the plasma was 65 per cent by volume (normal from 55 to 65). The treatment with alkali was discontinued for two days and then the patient was given 43 units (30 grams [1.95 Gm.]) per dose.

On March 14 he complained of crampy abdominal pain with gas and said the bowels felt as though they were "burning up." That night there were several watery brown stools. He complained of these symptoms more or less until he left the hospital. Enemas of physiologic solution of sodium chloride and phenolated solution of iodine gave some relief. On March 16, he was again given 55 units of alkali, because the aspirations remained acid practically all the time. The dosage of powder was increased to 65 units on March 19. On the next day, the carbon dioxide capacity was 65.9 and the blood chlorides 440. Aspirations to date totaled

1,150 cc, representing about 6 Gm of sodium chloride. There were no symptoms to suggest alkalosis. On March 21, supplementary feedings were started and he tolerated the 65 units without difficulty.

CASE 2—S. B., a white man, aged 30, had a condition that was diagnosed duodenal ulcer and irritable colon. The urine contained a slight amount of albumin on one occasion. The blood showed nonprotein nitrogen, 34.1, urea nitrogen, 16.3 (normal from about 12 to 15). Sippy treatment was started on Nov. 5, 1925, with 55 units of alkali. On November 7, the dosage of alkali was increased to 80 units. On November 8, the patient complained of a "shaky sensation," nausea and headache, and began to vomit. Aspirations had totaled only about 0.25 Gm of sodium chloride. The dose of alkali was reduced to 55 units, but he was still nauseated on November 9. The carbon dioxide capacity was only 63.5, so he was given 80 units per hour between 11:30 a. m. and 6:30 p. m. Headache, nausea, vomiting and weakness continued. Finally, on November 11, he was put on a bland diet with three feedings per day and 83 units of alkali an hour after meals and at bedtime. Two weeks later he reported that the symptoms of ulcer were gone, but he had a burning sensation in the epigastrium. The diagnostic fractional test meal had shown a free acid of from 72 to 116 units. The alkali may have further increased the acid secretion after the period of temporary neutralization and caused burning distress. The powder was increased to six doses per day.

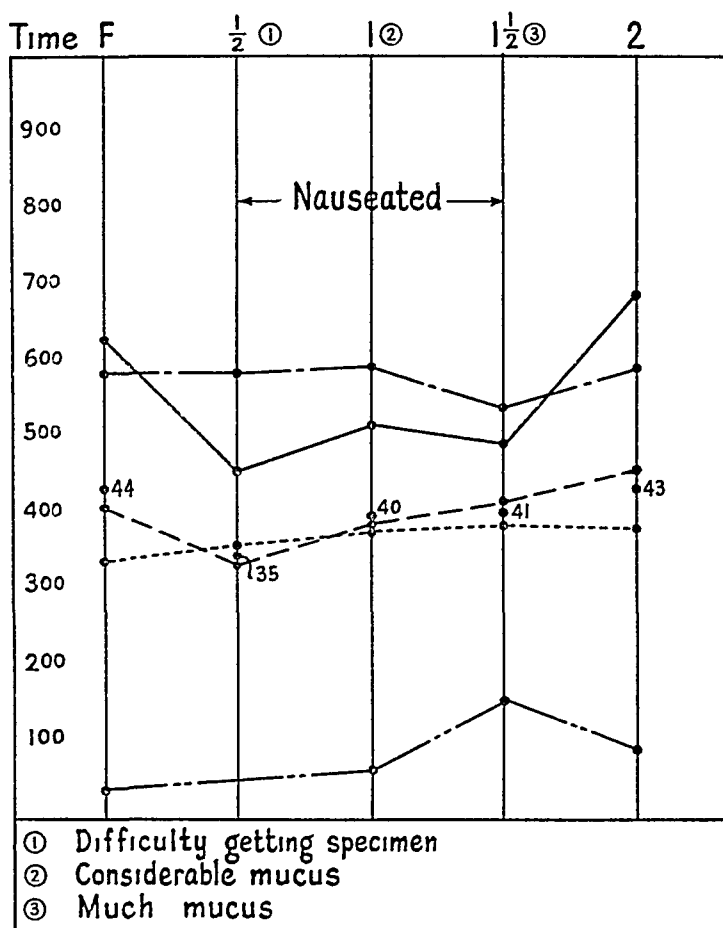
On Sept. 16, 1926, he returned with recurrent ulcer distress. He vomited that night. The next day the plasma chlorides were 570 and the carbon dioxide capacity 64.7, he was started on Sippy therapy with 55 soda units. The next day he had a headache and was irritable. The carbon dioxide capacity was 66.6. Because all aspirations were acid, the alkali was increased to 80 units on September 20. The urine was normal. The next day he felt that the cream did not "agree" with him. Whole milk was substituted for the mixture of equal parts of milk and cream. In twenty-four hours, the blood chlorides had dropped from 430 to 360 and the carbon dioxide had risen from 61.7 to 68.4. There was increasing nausea. By 4 p. m., the carbon dioxide capacity was 70.3, but the blood chlorides were reported as 390. The urea was 13.5. The intravenous injection of 500 cc of 5 per cent solution of sodium chloride cleared up the general feeling of heaviness, the distaste for food and other symptoms of alkalosis within five minutes, but he complained of excessive thirst, tightness in the chest and had chilly sensations for an hour. He then felt all right and began to take the powders and milk. The blood chlorides were now 460 and the carbon dioxide 66.6. The range of the temperature remained normal. Hourly samples of urine, from 5 to 9 p. m., showed the excretion of urea to be 2.6, 1.9, 0.87, 0.69 and 0.62 Gm, the excretion of chloride, 1.18, 1.62, 1.12, 0.42 and 0.41 Gm, consecutively. The phenolsulphonphthalein output of the kidneys was 60 per cent for two hours. At 9 p. m., the blood chlorides were 380, but the next day they increased to 420, with a carbon dioxide capacity of 62.7.

Because of the marked intolerance to alkali therapy, a gastro-enterostomy was done.

The accompanying chart shows the observations in a case of chronic hypochloremia. The blood chlorides were from about 15 to 20 per cent below normal, and had probably been subnormal to that degree for some time, in view of the symptoms of drowsiness, nausea, headache and weakness. The patient received Sippy treatment over a period of two years. He consulted me only for diagnosis.

Table 1, case 3, shows the record on a case of acute hypochloremia apparently resulting partly from chloride depletion and precipitated and aggravated by alkali.

CASE 3—J B, a man, aged 48, a foreman in a forge shop, had a condition of fifteen years' duration that was diagnosed ulcer, with a 75 per cent retention after six hours. He weighed 110 pounds (49.9 Kg), the ideal weight being 148 pounds (67 Kg). He had taken sodium bicarbonate for the relief of the condition. The kidney function was phenolsulphonphthalein return, 43 per cent in two hours. The urine showed a gravity of 1.012, without albumin. The blood showed hemoglobin, 109 per cent, and red blood cells, 4,550,000.



KEY { ——— Total gastric Cl. ——— Total acid Cl.  
 ..... Cell Cl. ° Cell volume percent.  
 - - - - - Whole blood Cl. ——— Plasma Cl.

J T, aged 23, had a condition that was diagnosed irritable colon and duodenal ulcer (healed) of seven years' duration. The patient was examined on Jan 26, 1926. In the chart all chlorides are expressed in the equivalent of sodium chloride in milligrams per hundred cubic centimeters.

*Alkalosis with Calcium Carbonate*—CASE 4—R M, a man, had a condition diagnosed duodenal ulcer and irritable colon. Ulcer therapy was started on May 17, with calcium carbonate, 20 grains (1.3 Gm) per dose. On May 20, the blood chlorides were 420 and the carbon dioxide capacity 66.6. The dosage of calcium carbonate was increased to 30 grains (1.95 Gm) per dose, because the free acidity was not neutralized. On May 21, the blood chlorides were 410, the carbon dioxide

capacity, 79.1, headache, nausea and lassitude, symptoms of alkalosis, obtained. To that date, aspirations from the stomach were small and there was no diarrhea<sup>22</sup> to deplete the reserve of chloride.

*Alkalosis with Sippy Powders*—CASE 5—B. B., a man, had a condition that was diagnosed duodenal ulcer. Sippy therapy was started on Feb. 27, 1927, with 55 units. On March 1, he had an uneasy feeling in the stomach and a dull headache. The next day, the headache disappeared, but the uneasy feeling in the stomach continued. The blood chlorides were 390, the carbon dioxide capacity, 83.8. Alkalis were discontinued, and on March 3 the carbon dioxide capacity was 68.4.

In table 2, case 6, the cause of the alkalosis is not clear. Other factors complicated the picture. This case was carefully studied.

CASE 6—O. M., a man, aged 48, a foreman in a lumber yard, had a condition diagnosed duodenal ulcer, with a retention of 100 cc. at 11 p. m., he had also a deformed appendix, secondary syphilis and chronic tonsillitis. He had taken sodium bicarbonate for relief from pain. The test for kidney function showed a phenolsulphonphthalein return of 70 per cent in two hours. On May 19, 1927, the urine had a gravity of 1.006, without albumin, on May 27, the gravity was 1.016, without albumin. On May 25, the blood showed 85 per cent hemoglobin, on May 30, 95 per cent hemoglobin and 4,250,000 red blood cells.

*Compensated Alkalosis*—CASE 7—R. T., a woman, had a condition that was diagnosed duodenal ulcer with partial pyloric obstruction. Sippy therapy was started on Jan. 14, 1927. The carbon dioxide capacity was 61.4, the blood chlorides, 445, and the urea, 12.1. On January 17, the carbon dioxide was 73 and the chlorides 470, on January 22, 71.9 and 440, respectively. The dosage of powder was then reduced to 40 units, and supplementary feedings were started. Apparently, aspirations had not been large enough to deplete the chloride reserve sufficiently to produce hypochloremia, and the alkalis caused no apparent disturbance of chloride metabolism. Not until after a week of therapy did the patient show definite improvement of the pyloric obstruction. On January 21, the aspiration at 11 p. m. yielded 180 cc., on January 24, 65 cc., and on the next day, 30 cc. No symptoms of alkalosis developed with the increase of carbon dioxide capacity. Therefore, apparently there was compensation throughout the course of treatment at the hospital.

In the following case, I do not understand the low carbon dioxide readings. A check determination by the central laboratory on June 14 gave a result similar to mine. My personal observations in this case, aside from the results tabulated, were negligible. The blood sugar was 74 mg. per hundred cubic centimeters (normal from about 80 to 85). The urine showed no albumin or sugar on several examinations, no tests were made for acetone bodies. Diabetes would complicate the relationship of the chlorides to the other observations, since the blood of diabetic patients has a low chloride content<sup>23</sup>. An inanition acidosis might account for the low readings—the patient lost 6 pounds (2.7 Kg.) in the week before treatment was started. There was no pyloric obstruction.

<sup>22</sup> Host, H. F. Chloride Metabolism, *J. Lab. & Clin. Med.* **5** 713, 1919-1920.

<sup>23</sup> Eisenman, A. J., Bulger, H. A., and Peters, J. P. Acid-Base Equilibrium Studies, *J. Biol. Chem.* **67** 219, 1926.

TABLE 1—Observations in Case 3

Date 8 a m	Blood				Gastric Contents					Twenty Four Hour Chlorides in Grams				Remarks			
	Cell Volume	Chloride as Mg. of Sodium Chloride per 100 Cc			Nonprotein Nitrogen and Urea	Carbon Dioxide Capacity	Phenolphthalein per Cent	Volume Test Content	Hydrochloric Acid		Total Sodium Chloride as Sodium Chloride	Output			Intake	Chloride Balance	
		Blood	Plasma	Cell					Free Units	Total as Sodium Chloride		Urine	Stool				Aspirations* (Estimated Sodium Chloride Equivalent)
5/17	0.50?	453	414	336?	29.4	6	25	100	32	14	257	540	0.75 (150 cc)			Admitted to hospital June 10 of belladonna, 20 m three times a day, phenobarbital, 0.5 grains three times a day, nuxem and vomiting during night, milk and cream, 4 ounces every quarter hour from 9 a m to 6 p m	
5/18	0.365?	444	527	299?	33.3 15.0		33	75	33	15	232	452	8.13 (1,625 cc) vomitus 7 cc	2.0			-13.1
5/19	0.42	490	581	364			20	70	32	10	234	571	9.0 (1,800 cc)	2.24			-8.2
5/20	0.42	459?	545?	340?		62	30	10	55	62	363	480	3.18 (635 cc)	2.24		-1.3	
5/21	0.40	324	416	186		61	17	70	23	30	176	488	4.73 (945 cc)	2.24		-2.6	
5/22	0.38	354	449	200	50.0 33.4	66	25?	35	12.5	18.7	169	577	0.45 (90 cc)	0.20	2.5	+ 1.6	
5/23		320			49.2 29.4										2.5		
5/23 (4 p m) 5/24 (8 a m)	460 320	Gastro enterostomy done on 5/25/27				53									16.0		
Sodium chloride given in divided doses between 8 a m and 4 p m																	

\* One hundred cubic centimeters of average contents was estimated to be equivalent to 0.5 Gm of sodium chloride

TABLE 2—Observations in Case 6

[illegible]

\* One hundred cubic centimeters of average contents  
† F denotes fasting contents, T, test contents

CASE 8—C A, a man, aged 46, had a condition that was diagnosed duodenal ulcer (without evidence of retention) Treatment for ulcer was started at 4 p m on June 13, 1927, with calcium carbonate, 20 grains (1.3 Gm) per dose On June 15, the dose was increased to 30 grains (1.95 Gm) No note was made of symptoms of alkalosis The observations are shown in table 3

TABLE 3—*Observations in Case 8*

Date	Time	Blood Chloride	Plasma Chloride	Urine Chloride	Nonprotein Nitrogen	Urea Nitrogen	Carbon Dioxide Content	Carbon Dioxide Capacity	pH
6/14/27	9 a m	440			35.7	14.9		44.5	
6/15/27	4 p m	410					43.85		7.38
6/16/27	9 a m	402	525	224	66.6	21.7	49.8	55.0	7.56
6/18/27	9 a m	444	536		36.3	21.0	46.4	49.5	7.52

## COMMENT

The study of these and other cases convinces me of the importance of chloride metabolism in a treatment for ulcers. The intake of chlorides by patients on the Sippy milk diet without supplementary feeding is low—about 2 Gm instead of the optimum of 5 Gm or so per day—although an intake of only 1.25 Gm per day for several weeks has been tolerated<sup>24</sup>. Therefore, the Sippy milk diet probably supplies enough chlorides unless there is disturbance by the alkalis or depletion by vomiting, aspirations or diarrhea<sup>22</sup>. In spite of the success of Molnár and Csaki<sup>25</sup> in controlling cases of simple hyperacidity by the restriction of the chloride intake, I favor, if anything, the addition of small amounts of sodium chloride to the powders and milk of patients on the Sippy treatment to insure a positive balance until supplementary feedings are started. There must be a marked depression of chloride reserve before gastric secretion is affected. I believe from 5 to 10 Gm of sodium chloride daily will serve as a prophylactic against depletion and disturbances of chloride balance by alkali. Ammonium or calcium chloride must not be used for reasons considered later.

Sodium chloride is of value in the treatment of some patients with alkalosis. It is of greatest benefit in cases like 1 and 2. Results are fair in patients with marked depletion (case 3), and sodium chloride is of no definite benefit to patients with little or no depression in the amount of blood chlorides (case 6).

In my cases of ulcer there seemed to be four types of alkalosis. In the uncompensated type were found (1) those persons with normal plasma carbon dioxide capacity and a hypochloremia which results from

24 Mayer, A. Observations on the Urine with Salt-Poor Diet, *Compt rend Soc de biol* 58 377, 1905

25 Molnár, B., and Csaki, L. Hyperacidity as a Disturbance of Chloride Metabolism, *Ztschr f klin Med* 100 239, 1924, abstr., *J A M A* 83 77 (July 5) 1924

the alkalis themselves (cases 1 and 2) or partly from the depletion of a pyloric obstruction (case 3), (2) those with high carbon dioxide capacity and hypochloremia (cases 4 and 5), (3) and possibly a type with no distinct change of carbon dioxide or chloride content (case 6—only one case like this) (4) The compensated type has no symptoms referable to alkalosis, and the carbon dioxide content is high with normal amounts of chlorides (case 7) The patients with chronic alkalosis have a normal carbon dioxide content and hypochloremia (chart 1) The patient with a chronic case with adequate quantities of chlorides in the supplementary feedings would probably not be benefited by further additions of sodium chloride In the uncompensated type, the intravenous injection of physiologic solution of sodium chloride gives prompt results, however, care must be taken not to give doses too large, too frequently or in too concentrated a form, lest excessive thirst, tightness in the chest, contraction and burning of the throat and chilly sensations or pyrexia, symptoms of acute hyperchloremia, set in (case 2) The total amount required may be gaged somewhat by the estimated chloride deficit (tables 1 and 2) A secondary fall of blood chlorides several hours after an injection may be expected, and sodium chloride should be given until the symptoms of alkalosis have disappeared or a normal equilibrium of blood chlorides is reached Care must be taken not to go too far beyond this point, lest disturbed kidney function, edema, nausea and vomiting, marked sinus bradycardia and lowered blood pressure, signs of "chronic" hyperchloremia, set in

In the laboratory diagnosis of alkalosis, the plasma carbon dioxide capacity<sup>24</sup> is not a criterion of alkalosis, neither is the carbon dioxide content<sup>26</sup> The former is normally a little bit higher Both are elevated in some types of alkalosis (cases 4 and 5), with a proportionally greater difference in the greater degrees of alkalosis (case 8) In patients with symptoms of alkalosis, I found, with one exception (case 6), an unusual depletion of blood chlorides, especially in the cells (chart 1) In the case not following this rule, I believe a simultaneous determination of carbon dioxide content and capacity would have revealed a difference greater than normal, thus suggesting an increased ratio of basic carbonates to carbonic acid, which in turn indicates an increased  $p_{\text{H}}$ , the true measure of alkalosis Accurate  $p_{\text{H}}$  determinations<sup>27</sup> are difficult to make unless one is doing a number of them regularly In compensated cases with high carbon dioxide readings, one might find a normal difference between the capacity and content

26 Van Slyke, D. D., and Neill, J. M. Determination of Gas in Blood by Vacuum Extraction and Manometric Measurement *J Biol Chem* **61** 523, 1924

27 Hastings, A. B., and Sendroy, J. Colorimetric Determination of  $p_{\text{H}}$  without Buffer Standards, *J Biol Chem* **61** 695, 1924 Cullen, G. E., and Büllmann, E. Quinhydrone Electrode for Hydrion Determination in Serum, *J Biol Chem* **64** 727, 1925



The capricious variations of blood chlorides following intravenous injections of sodium chloride indicate that one can tell nothing about the chloride reserve of the body by a simple analysis of the blood for chlorides. One can tell little more by following the chloride balance day after day. There is the suggestion of a shift in body chlorides caused by the alkalis (table 1), but where the storage places are is as puzzling as in the chloride retention of pneumonia<sup>22</sup> in which the chlorides are also low<sup>23</sup>. The skin may take up a large part of it<sup>28</sup>. The urine seems to be the most sensitive indicator of approaching alkalosis (the drop in the chloride of the urine should be noted in tables 1 and 2), but does not suggest the status of the chloride reserve or the blood chlorides. The amount excreted in the stools is negligible and suggests that calcium carbonate does not reduce the absorption of chloride<sup>29</sup>.

The odd change in the gastric response accompanying alkalosis is apparently due to the systemic action of alkali. In the case in table 1, I do not understand the rise and drop in free and total acid without an accompanying change in the total gastric chlorides. There is a similar rise and drop in the acid of the contents of the stomach while fasting in the case reported in table 2, but in the test contents the acid rises with a slight drop on May 28 and a greater drop on May 30. In studying the acid secretion of several patients with ulcers, I thought I could detect, in the routine aspiration at 4 p. m., 9 p. m. and 11 p. m. (in patients with retention) a tendency of the acid secretion to rise the day before the symptoms of alkalosis occurred. This was particularly true of the aspiration at 11 p. m., which may be taken to represent the contents of the stomach while fasting. When alkalosis occurred, the acid secretion was much reduced. These changes were not constant or definite enough to be of value in detecting the tolerance point to alkali. Careful weighing of the evidence indicates that the local action of alkali, the local or systemic action of belladonna given to these patients and gastric fatigue played little, if any, part in the reduction of the acid secretion. In case 3, the depletion of chloride may have played a part and the alkalis precipitated and aggravated the condition.

A study of the dilution of phenolphthalein in the test meal<sup>30</sup> yielded no observations of definite value. Table 1 shows a slight rise in the percentage of phenolphthalein when nausea began and a fairly marked drop when the administration of alkali was discontinued because of alkalosis. Without characteristic changes in volume, these observations are

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28 Sollman, Torald. *A Manual of Pharmacology*, ed 2, Philadelphia, W. B. Saunders Company, 1922, p. 777.

29 Goldschmidt, S., and Bingers, C. A. L. Effect of Calcium on Intestinal Absorption of Sodium Chloride, *Am. J. Physiol.* **48** 473, 1919.

30 Gorham, F. D. Factor of Dilution in Gastric Analysis. *J. A. M. A.* **41** 1738 (Nov. 24) 1923.

difficult to interpret. The increased percentage with the onset of nausea might indicate a slower emptying of the stomach. This suggests also a decrease of the volume of secretion, as the volume of contents is about the same or lower. The fairly low percentage and drop of volume when the doses of alkali were discontinued may mean that the pyloric obstruction was beginning to yield to treatment. In case 6, a rise occurred when alkalosis appeared, however, with the presence of epigastric pain, it was thought that the ulcer rather than the alkali might account for most of the symptoms, so the alkali therapy was not discontinued. Therefore, the percentage of phenolphthalein remained high. The increases in volume in the first two days of symptoms suggest that the delay of the emptying time was playing a large part in the result, but the third day the drop in volume hints that there was a decrease of secretion. It is preposterous to try to estimate the volume<sup>31</sup> of secretion in an aspiration made after an interval of half an hour, when one considers that on the last day the patient in case 3 would have secreted 1,920 cc. in the half hour interval, and the one in case 6, 3,950 cc. in that time on the first day.

The blood urea and nonprotein nitrogen seemed to increase only when there was a marked depletion or when the alkalosis was marked or prolonged. The intravenous injection of physiologic solution of sodium chloride increased the excretion of urea in case 2, but not much of the salt was poured out into the urine. Apparently, my cases were not profound enough to give evidence of kidney disturbance, and damaged kidneys played no part in precipitating the alkalosis.<sup>9</sup>

With a clear picture of the symptoms and observations in my cases, I shall now consider the problem of the pathogenesis of alkalosis. Whether there is chloride privation,<sup>5</sup> depletion<sup>32</sup> or depression by alkalis,<sup>11</sup> the symptoms are much the same. I therefore feel justified in ascribing much of the symptomatology to the hypochloremia which results. The unquestionable shift in balance between tissue and blood chlorides profoundly affects the nervous system, the vegetative portion of which seems to give the most positive signs of alkalosis. An upset in the balance between the sympathetic and the parasympathetic divisions can be made to explain many of the symptoms. I believe that in alkalosis there is a primary stimulation of the sympathetic system followed by a depression. To stimulation one may ascribe the warm,

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31 Keefer, C. S., and Bloomfield, A. L. Clinical Study of Gastric Function, J. A. M. A. 88:707 (March 5) 1927.

32 Haden and Orr and MacCallum (footnote 3) Hastings, Murray and Murray (footnote 11) Houghton (footnote 12)

33 Hardt and Rivers (footnote 2) Jordan (footnote 7) Grant (footnote 8) Venables (footnote 9)

dry skin, the primary state of restlessness, nervousness, irritability, diarrhea, decreased respiration (which may be due to the increased capacity of the blood to carry carbon dioxide) and rapid pulse. The sympathicotonic person is said to have a tendency toward deficient acidity, a warm dry skin, a rapid pulse, is lively, excitable, has a rosy color, mobile dilated pupils, a fairly moist throat and a diminished or absent oculocardiac reflex. He is sensitive to epinephrine, pituitary extract and thyroid.<sup>34</sup>

In the more toxic state in alkalosis there are marked mental dulness and stupor, muscular twitchings, marked sweating, slow pulse and marked nausea and vomiting. The last four of these symptoms are more apt to be found in the vagotonic patient, who is said to be cold-blooded and reserved, and often to have a low blood pressure, contracted pupils, deep-set eyes, slow pulse and a sensitive oculocardiac reflex. He has a tendency to gastric hyperacidity, nausea and vomiting and his cool, pale skin sweats easily. Respiratory arrhythmia, asthma, spastic constipation, high sugar tolerance and eosinophilia are said to be common among vagotonic patients.<sup>35</sup> The vagus may predominate in the profound degrees of alkalosis because of sympathetic depression.

The paresis of the posterior extremities observed by Frouin<sup>5</sup> in dogs suggests that the hypochloremia profoundly affected the spinal cord. The sympathetic centers in the intermedio-lateral columns may be affected by the same process. Several of my patients were given tincture of belladonna, but only in case 3 were there effects from atropine, as was indicated by a dry throat. I am sure that belladonna played little part in the production of the symptoms noted.

In acute hyperchloremia the tight feeling in the chest and the contraction of the throat may result from marked stimulation of the vagus, reminding one that the vagotonic patient is prone to have asthma. In chronic hyperchloremia, I do not believe that the vomiting, sinus bradycardia and lower blood pressure are due to vagus stimulation alone, although the vagotonic patient has a tendency to nausea and vomiting, slow pulse and low blood pressure. I do not know whether kidney dysfunction is primary or secondary, but surely it is aggravated and prolonged by the overload of chlorides.

In patients with definite hypochloremia (below 420), there were lassitude, restlessness, a dull feeling in the head, irritability, distaste for food, nausea and vomiting, dulness, weakness, "shaky sensations," and

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34 Purves-Stewart. *Diagnosis of Nervous Diseases*, ed 6, London, Edward Arnold and Company, 1924, p. 445.

35 Eppinger and Hess. *A Clinical Study in Vegetative Neurology* (Monograph on Vagotonia), New York, Nervous and Mental Disease Publishing Company.

in one case a craving for salt. The secretion of acid was diminished and the volume of secretion seemed to be lessened. In chronic alkalosis, there were weakness and cramps in the legs, diarrhea, dyspnea on exertion and other signs of weakness. Floum,<sup>5</sup> experimentally, obtained lassitude, irritability, loss of appetite, dulness, muscular weakness, achlorhydria, trembling, paresis of the posterior extremities, convulsions with fits of anger and diminished volume of gastric secretion. What a close parallel to the symptoms found in clinical cases, even to the achlorhydria toward which case 3 was progressing rapidly when salt solution was given! If one allowed the hypochloremia to become profound enough or last long enough one might get paresis of the legs and tetany.<sup>8</sup> When  $p_H$  readings were taken, they ranged from about 7.52 to 7.64 (the upper limit of normal being 7.47<sup>15</sup>), and thus were well below 7.8 the point at which tetany occurs.<sup>19</sup>

The question of the salts most useful in alkali treatment has been reviewed in this study. Potassium salts<sup>36</sup> may at once be dismissed because of their toxicity and high cost. Sodium salts have already proved their value, but in spite of the fact that soda gives more rapid relief, its action is not so prolonged, it seems to produce diarrhea in some cases and it is so readily absorbed that it appears to produce alkalosis more easily.<sup>37</sup> The importance of sodium chloride has already been discussed.

Calcium salts have proved their usefulness, but are not without fault. In spite of the fact that the carbonate is said not to be so readily absorbed,<sup>37</sup> it can produce alkalosis on doses little, if any, higher than those with the mixed powders of Sippy (neutralizing power of calcium carbonate two and a half times that of soda). I have no comparative studies to show the relative ease with which each salt might produce alkalosis in a given case. Several times at this hospital I have noted calcified concretions in the appendixes of patients who have taken calcium carbonate for gastro-intestinal conditions. Although most of the calcium is said to be excreted in the stools, some of Jordan's cases<sup>7</sup> showed distinct rises of blood calcium. Perhaps these are the persons in whom alkalosis from calcium carbonate is more prone to develop.

This salt is said to have a constipating action, however, this fact is denied by Loevenhart and Crandall.<sup>38</sup>

In spite of objections, I believe calcium carbonate is to be preferred. When I compare cases 3, 4 and 6 with cases 1, 2 and 5, I believe that alkalosis occurs less readily by the omission of soda. Surely, the hypo-

36 Sollman (footnote 28, page 787)

37 Loevenhart, A. S., and Crandall, L. A. Calcium Carbonate in Treatment of Hyperacidity, *J. A. M. A.* 88 1557 (May 14) 1927. Myers and Gatewood (footnote 17)

38 Loevenhart and Crandall (footnote 37, first reference)

chloremia seems to be less and the symptoms of alkalosis not as acute. Perhaps the chlorides were made more stable by the use of calcium carbonate alone. Perhaps calcium salts might help to prevent tetany,<sup>39</sup> for de Geus<sup>39</sup> did not obtain tetany with a blood calcium above 8 mg per hundred cubic centimeters unless there was an excess of sodium. This means that if attempts are made to treat medically persons who have the milder degrees of pyloric obstruction, it is best to omit sodium bicarbonate, and that it would be justifiable to use small amounts of calcium chloride with the sodium chloride and dextrose in severe cases in which the patients are being prepared for operation.

Other arguments for the use of calcium carbonate are its greater and more prolonged neutralizing power. In spite of still greater neutralizing power and laxative properties, magnesium oxide should be condemned for use in the powders. With its use I have had irritable colon and chronic colitis develop in cases in which they did not exist before. Other means should be used to keep the bowels regular, such as mineral oil, stimulating enemas of cool water or oil retention enemas, suppositories, and, later in the treatment, additions to the diet.

With regard to the most desirable acid radical in the alkaline salts, the carbonates have been the most favored, as well they might be. They are less toxic and more effective than others which might be used. Phosphates have been used, but have given only fair results because of their extremely low neutralizing value and very slow action.<sup>40</sup> Citrates have been used in very small doses in the treatment for peptic ulcer.<sup>41</sup>

Both acid and basic chlorides are lost in aspirations and vomiting. Sodium chloride can therefore make up only part of the deficit, and thus accounts for the partial success in depletion (table 1). Youmans<sup>42</sup> and others have used ammonium chloride, theoretically the ideal salt, because the liver converts the ammonium ion into urea, leaving the chloride ion free to make up the disproportionate deficit of chloride. But this action of the liver protects the body against the toxic ammonium ion which makes patients with alkalosis feel worse. Given by mouth the general circulation is better protected, but the nauseating taste contraindicates its use by this route. The livers of patients with ulcers are frequently damaged and I believe it unwise to impose this extra burden. A patient with sprue (?) with alkalosis complained of severe contraction and burning of the throat, and said "everything turned

39 De Geus, J. G. F. Tetany and Alkalosis, *Nederl maandschr v Geneesk* **13** 361, 1926, abstr, *J A M A* **86** 1955 (June 19) 1926.

40 Shattuck, H. F., Rohdenburg, E. L., and Booher, E. E. Antacids in Medical Management of Ulcer *J A M A* **88** 200 (Jan 19) 1924.

41 Vanderhoof, D. Medical Cure of Duodenal Ulcer, *J A M A* **89** 344 (July 30) 1927.

42 Youmans, J. B., and Green, F. W. Treatment of Gastric Tetany with Ammonium Chloride, *J A M A* **84** 808 (March 14) 1925.

black" when she was given ammonium chloride intravenously according to the method of Youmans. There may be a judicious balance between sodium and ammonium chlorides, permitting their use together with better results than either one singly.

Calcium chloride must be used judiciously—when used in the case just mentioned to stop tetany it produced burning of the hands, feet and rectum, a hot feeling all over, vomiting, grasping for breath, irregular pulse rate and for two days a lower range in temperature. On account of its disagreeable taste, I do not believe that calcium chloride should be given by mouth.

#### SUMMARY AND CONCLUSIONS

Much more work is needed to settle the questions raised by this study, but the following deductions are suggested by the observations thus far:

1. There must be a marked reduction of the chloride reserve in the body before gastric secretion is definitely affected, and then there is a drop in the free and the total acid without the reduction of the total chlorides, accompanied by the symptoms of alkalosis. The systemic action of the alkali used in the treatment for peptic ulcer apparently precipitates and aggravates this reaction. There is a vague suggestion of decreased volume of secretion. The acid secretion of patients with peptic ulcer cannot be controlled by restriction of the chloride intake.<sup>43</sup>

2. In cases of alkalosis without such profound depletion there is a suggestion of a similar phenomenon, particularly in the "fasting" contents.

3. A patient might remain on the Sippy milk diet indefinitely without chloride depletion, but in patients with nausea and vomiting, diarrhea or pyloric obstruction, one must take into account and make up the chloride deficit by giving sodium chloride if one expects the patient to continue to tolerate alkalis. Calcium and ammonium chlorides, if used at all, should be used sparingly and only after consideration of indications and contraindications in the individual case.

4. Alkali therapy might tend to decrease the free and the total acid secretion of the stomach while fasting, but longer periods of study are necessary to determine whether the gastric response to stimulation of food and alkali is definitely affected.

5. If it were possible to get samples of gastric contents free of mucus, saliva and duodenal regurgitation, one might get more definite relationships between total acid chlorides and total gastric chlorides, but present methods preclude this possibility.

6. A study of the relationship of the excretion of chloride to blood chlorides has not given a definite idea of the chloride reserve of the

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<sup>43</sup> Weitz, W., and Kissling, W. Chlorides and Hyperacidity, *Munchen med Wchnschr.* **72** 2177, 1925, abstr., *J. A. M. A.* **86** 455 (Feb. 6) 1926.

body, but the urine chlorides are markedly decreased when there is hypochloremia, which is an early sign of approaching alkalosis. Chloride excretion in the stools is negligible and does not suggest diminished absorption of chlorides from the use of calcium carbonate.

7 When the secretion of gastric acid is reduced in hypochloremia, the ratio of cell to plasma chlorides is reduced. A similar reduction of tissue cell to tissue fluid chloride, especially in sensitive nerve cells, may be the basis of the symptoms of alkalosis. I therefore, feel justified in ascribing symptoms to the effect of the hypochloremia which is a common accompaniment of uncompensated alkalosis—only one of my patients failed to have low blood chloride values, and here the picture was not clearcut on account of the symptoms of accompanying conditions.

8 In hypochloremia there may be a normal carbon dioxide capacity of the plasma with symptoms commonly ascribed to alkalosis. Therefore, the carbon dioxide capacity is not a reliable index of alkalosis. When determinations of the carbon dioxide capacity and content are taken simultaneously, the former is a little bit the higher. Both are elevated in profound or prolonged hypochloremia with a proportionately greater difference between the two. The  $p_H$  is increased.

9 The occasional patients reacting to alkali therapy with hypochloremia and normal carbon dioxide capacity commonly have functional gastro-intestinal disturbances and probably have unusually sensitive vegetative nervous systems.

10 In one of these cases, sodium chloride given intravenously promptly cleared up the symptoms of alkalosis. In patients with chloride depletion the results are not so clearcut, and in a patient with normal blood chlorides the results were disappointing.

11 Patients with hypochloremia with symptoms of alkalosis were noted by the neuropsychiatrist to be "sympathicotonic," or to have "probable dysfunction of the vegetative nervous system." Symptoms of hypochloremia and alkalosis may be explained on the basis of primary stimulation of the sympathetic nervous system followed by depression in the more toxic states.

12 Some symptoms, such as weakness and cramps in the legs, with the previously mentioned condition of the vegetative nervous system suggest toxic action on the lateral columns and funiculi of the spinal cord.

13 Even patients with partial pyloric obstruction respond very well to the Sippy alkali treatment. I believe his general plan of treatment to be without a peer, and consider calcium carbonate used alone the alkali of choice. From six to eight weeks of intensive therapy with gradual reduction of powders and return to normal diet in about a year seems to suffice if all foci of infection are cleared up.

# CUTANEOUS AND VENOUS BLOOD SUGAR CURVES

## II IN BENIGN GLYCOSURIA AND IN DIABETES <sup>1</sup>

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M K ROSENBAUM

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AND

J P PETERS, M D

NEW HAVEN, CONN

As early as 1856, Chauveau <sup>1</sup> reported that there was more dextrose in arterial than in venous blood. Although his observations were known to Bang <sup>2</sup> and have been amply confirmed by subsequent investigators,<sup>3</sup> their implications have been almost entirely overlooked by most clinical observers especially in this country.

It has been definitely established by Hagedorn,<sup>4</sup> Foster <sup>5</sup> and others that in the normal person in the postabsorptive state arterial (or cutaneous <sup>6</sup>) and venous blood differ little, if at all, in their sugar content. After a meal containing carbohydrate, however, the sugar curve of the arterial blood rises more than that of the venous blood. A definite positive arterial-venous difference is established. This difference is the most direct evidence that the tissues are actively removing dextrose from the blood and that this process of removal is rapid enough to be easily measurable.

In an earlier communication <sup>7</sup> we described a procedure for the determination of alimentary cutaneous and venous blood sugar curves and its application to certain clinical and physiologic problems. Venous and cutaneous bloods, obtained as nearly simultaneously as possible.

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\* Submitted for publication, Oct 1, 1928

1 Chauveau. *Compt rend Soc de biol* **42** 1008, 1856

2 Bang, Ivar. *Der Blutsucker* Wiesbaden 1913

3 Hagedorn, H C. *Ugeskr f Laeger* **82** 796, 1920. Foster G L. *J Biol Chem* **55** 291 and 303, 1923. Holst, J E. *Hospitaltid*, Copenhagen, 1922, vol 65 p 577. Lawrence, R D. *Brit M J* **1** 516, 1926. Rabinowitch, I M. *Brit J Exper Path* **8** 76, 1927. Friedenson, Myer, Rosenbaum, M K. Thalheimer, E J, and Peters, J P. *Cutaneous and Venous Blood Sugar Curves I*, *J Biol Chem* **80** 269, 1928

4 Hagedorn (footnote 3, first reference)

5 Foster (footnote three, second reference)

6 Both Hagedorn and Foster have shown that as far as sugar content is concerned arterial and cutaneous blood are practically identical

7 Friedenson, Rosenbaum, Thalheimer and Peters (footnote 3, sixth reference)



were analyzed for dextrose by a micromodification of Benedict's<sup>8</sup> blood sugar method, reported in 1925, before, and at half hour intervals after, a meal consisting of either 50 Gm of dextrose or mixed foods containing from 75 to 110 Gm of carbohydrate. The effects of the two types of meals were not distinguishable.

It was found that the arterial-venous difference during fasting was usually negligible, but might be considerable. If a difference did occur it was usually positive (arterial > venous), although negative (venous > arterial) differences were occasionally observed. At either thirty or sixty minutes after the meal, or both, a positive difference, varying in magnitude from 6 to 50 mg per hundred cubic centimeters, was always encountered, generally coinciding with the highest blood sugar determination. This difference was found even when hyperglycemia was minimal. After ninety minutes, when two thirds of the curves had returned within the normal fasting range, the arterial-venous difference had usually disappeared and occasionally had become negative.

It was found that insulin, given to a normal person during fasting, usually caused a demonstrable positive difference during the hypoglycemic state.

A group of patients with disease of the liver showed excessive or prolonged hyperglycemic reactions, but normal arterial-venous differences. This was interpreted as evidence of impairment of the ability of the liver to remove dextrose from the blood for storage as glycogen, without disturbance of the mechanism for the mobilization of dextrose into the muscles and other tissues.

Holst<sup>9</sup> and Lundsgaard and Holboll<sup>10</sup> claimed that the arterial-venous difference cannot be demonstrated in diabetic patients after meals, but is restored by the administration of insulin. Rabinowitch<sup>11</sup> showed that this is not an absolute distinguishing feature of diabetes. He found differences in certain mild cases of diabetes. These differences, however, were in general smaller than normal, and were often entirely lacking.

In the present paper are described the arterial (cutaneous) and venous blood sugar curves of diabetic persons, with and without insulin therapy, and of patients with glycosuria of doubtful nature.

Chart 1 shows sixteen experiments on fourteen patients with so-called benign glycosuria. One patient (case 12) has not returned for observation. The fact that he had hyperglycemia during fasting and excessive alimentary hyperglycemia suggest that he was diabetic in spite of the fact that the curve returned to a normal or relatively hypoglycemic level.

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8 Benedict, S. R. *J Biol Chem* **64** 207, 1925.

9 Holst (footnote 3, third reference).

10 Lundsgaard, C., and Holboll, S. A. *J Biol Chem* **65** 323, 1925.

11 Rabinowitch (footnote 3, fifth reference).

at the end of ninety minutes EV (case 7) evidently developed an excessive prolonged hyperglycemia after the ingestion of food, and the glycosuria was not entirely unresponsive to dietary influences. Nevertheless, even in the postabsorptive state, when the blood sugar was within the normal fasting range, sugar was found in the urine. The

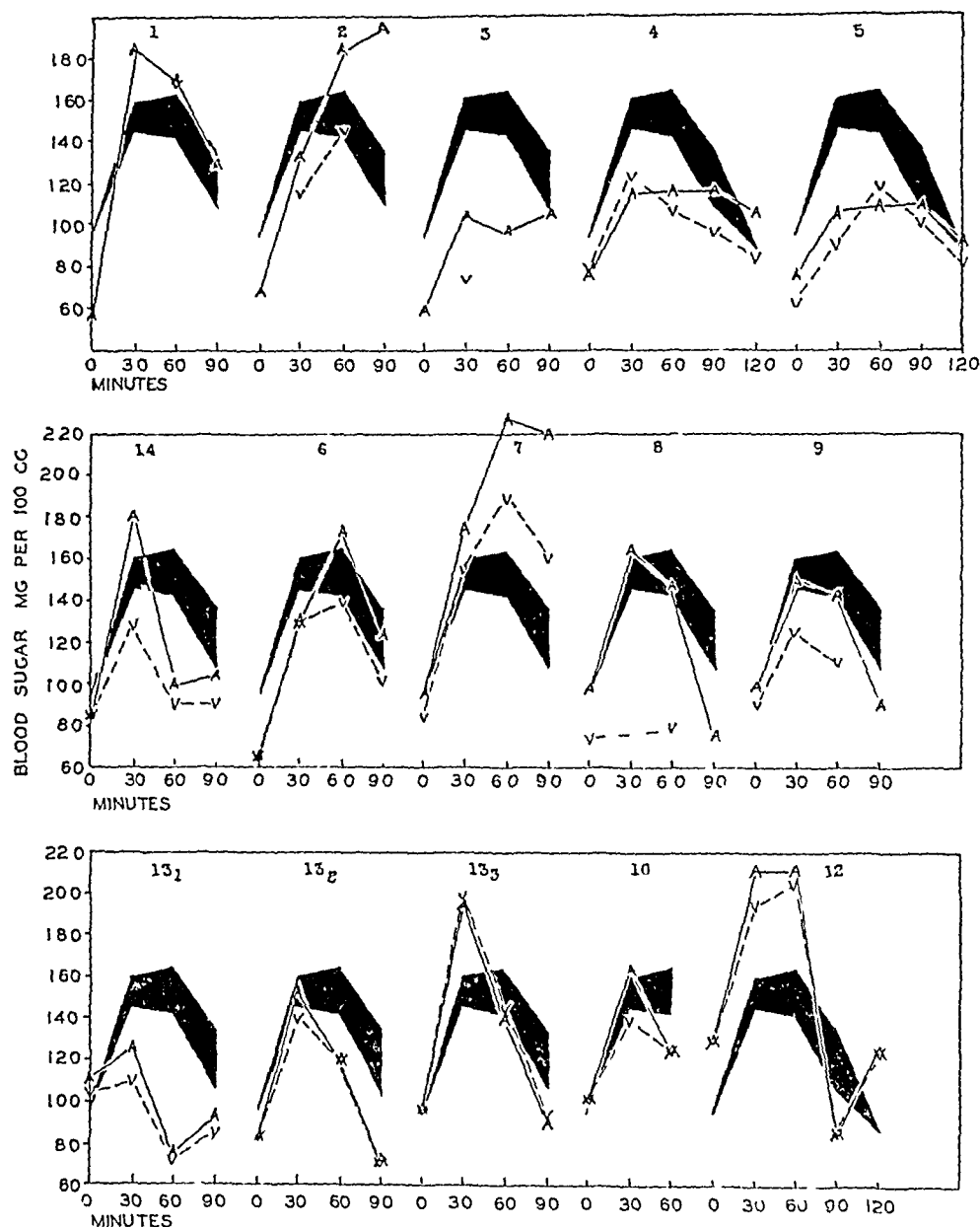


Chart 1—Blood sugar curves of patients with borderline glycosuria. A—A and V—V represent cutaneous and venous blood sugar curves, respectively. The solid area shows the normal limits as determined in this laboratory (Benedict J Biol Chem 64 207, 1925). The upper border of the area gives the highest observed cutaneous values, the lower border, the highest observed venous values. The case numbers are given above the curves.

long duration of the glycosuria without the appearance of diabetic symptoms and its relative failure to respond to dietary measures are evidence that it is nondiabetic and belongs to the class of "cyclic renal

glycosurias" described by Hatlehol<sup>12</sup> All these patients, whether diabetic or not, developed distinct arterial-venous differences

Only one case of the group (RW, case 5), seems rightfully to belong in the class of renal glycosurias Although this patient's curve is somewhat prolonged, it never rises above the range of normal alimentary hyperglycemia Nevertheless, he showed glycosuria both before and after the meal He developed a small, but distinct, arterial-venous difference at the end of thirty minutes If only the venous curves of cases 14 and 6 were taken into consideration, it would be easy to conclude that the hyperglycemic reactions were normal If glycosuria had occurred, it would have been as easy to conclude that it was of renal origin However, the arterial curves in both cases rose distinctly higher than those of the normal persons in whom investigations were conducted by the same method

It must be obvious that, if an arterial-venous difference is characteristic of the alimentary hyperglycemic reaction, a diagnosis of "renal glycosuria" cannot be made from studies of venous blood sugar alone, as has been the custom in this country This is especially true if the glycosuria is of the cyclic type, i e, if it occurs only after the ingestion of carbohydrate It is presumably the concentration of dextrose in the blood that goes to the kidneys and not that which comes from the tissues that determines the excretion of sugar in the urine Hatlehol<sup>12</sup> also called attention to the fact that the peak of alimentary hyperglycemia may be extremely evanescent It is, therefore, necessary not only to examine cutaneous blood, but to examine it at short intervals (every two to ten minutes) to establish a diagnosis of cyclic renal glycosuria in a person who does not show glycosuria in the postabsorptive state

It is also evident that certain subjects may, without the appearance of glycosuria, develop excessive or prolonged alimentary hyperglycemic reactions that manifest themselves only in the cutaneous blood sugar curves

According to all the usual criteria, the patient in case 13 had benign glycosuria Over a period of more than three years, sugar was found in the urine at intervals after meals, however, he never had symptoms of diabetes The blood sugar during fasting was repeatedly determined and almost invariably fell within the normal range, although his diet was never restricted In the three studies made on this subject, the alimentary hyperglycemic reaction was completed within ninety minutes, and in only one did the blood sugar reach an excessively high level In spite of all these indications that the glycosuria was benign and not of the diabetic type, he developed little arterial-venous difference In fact,

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<sup>12</sup> Hatlehol, R Acta med Scandinav, 1924, supplement 7

at the time he had the excessive hyperglycemia, he presented a persistent negative difference. Current theories, which hold that insulin affects especially the mobilization of sugar into and its utilization by the tissues, would lead one to conclude that these phenomena were evidences of a true diabetic state or lack of insulin. In the postabsorptive state, when the subject was given 10 units of insulin a striking degree of hypoglycemia and distinct symptoms of insulin shock develop, manifestations of an unusual susceptibility to the pancreatic hormone. Two hours after the dose of insulin and after he had taken considerable carbohydrate to overcome its effect, he showed moderate hyperglycemia and a positive arterial-venous difference of 25 mg.

The simultaneous studies of cutaneous and venous blood sugar curves have not, therefore, proved of great assistance in differentiating benign from diabetic glycosuria. They have demonstrated that determinations of the cutaneous blood sugar are of more value than those of the venous blood sugar in such differentiation. In fact, it is doubtful whether much significance can be attached to venous curves unless they show definite hyperglycemia. Certainly, determinations of the cutaneous blood sugar are far more reliable diagnostic measures.

Chart 2 presents the results of fifteen studies of ten patients with diabetes. Cutaneous and venous curves were obtained usually after the ordinary mixed breakfast of the diabetic diet. In two mild cases, 50 Gm of dextrose was given instead. In only two instances did the patients exhibit a significant degree of glycosuria, although none received insulin during the test. All the subjects had definite hyperglycemia during fasting, in spite of the fact that they had been on limited diets before the experiments.

All but two of the subjects showed large arterial-venous differences after meals. The two who failed to show such differences were, oddly enough, those with the smallest hyperglycemic reactions and with decreased blood sugar during fasting (cases 17 and 18). The magnitude of the arterial-venous difference cannot be used, therefore, as a criterion of the severity of a diabetic condition, nor is the failure to show such a difference characteristic of diabetes.

It is interesting to note that in the two mild cases of diabetes mentioned, cases 17 and 18, improvement of the diabetic condition was marked by an increase in the arterial-venous difference rather than by any change in the degree or duration of the arterial hyperglycemic reaction. In case 19, with improvement the difference increased and the hyperglycemia diminished.

Although large arterial-venous differences occurred in the most extreme hyperglycemic reactions, they presented certain peculiar characteristics not observed in normal persons, borderline cases or extremely mild cases of diabetes. In cases 23 and 24 the curves showed

differences of considerable magnitude at the end of thirty minutes. At the end of sixty and of ninety minutes, these differences had been almost entirely abolished, although the arterial hyperglycemia had not diminished or had even increased. The ability of the tissues to remove sugar from the blood in these patients, although not entirely lost, appeared to be limited in extent and was rapidly exhausted.

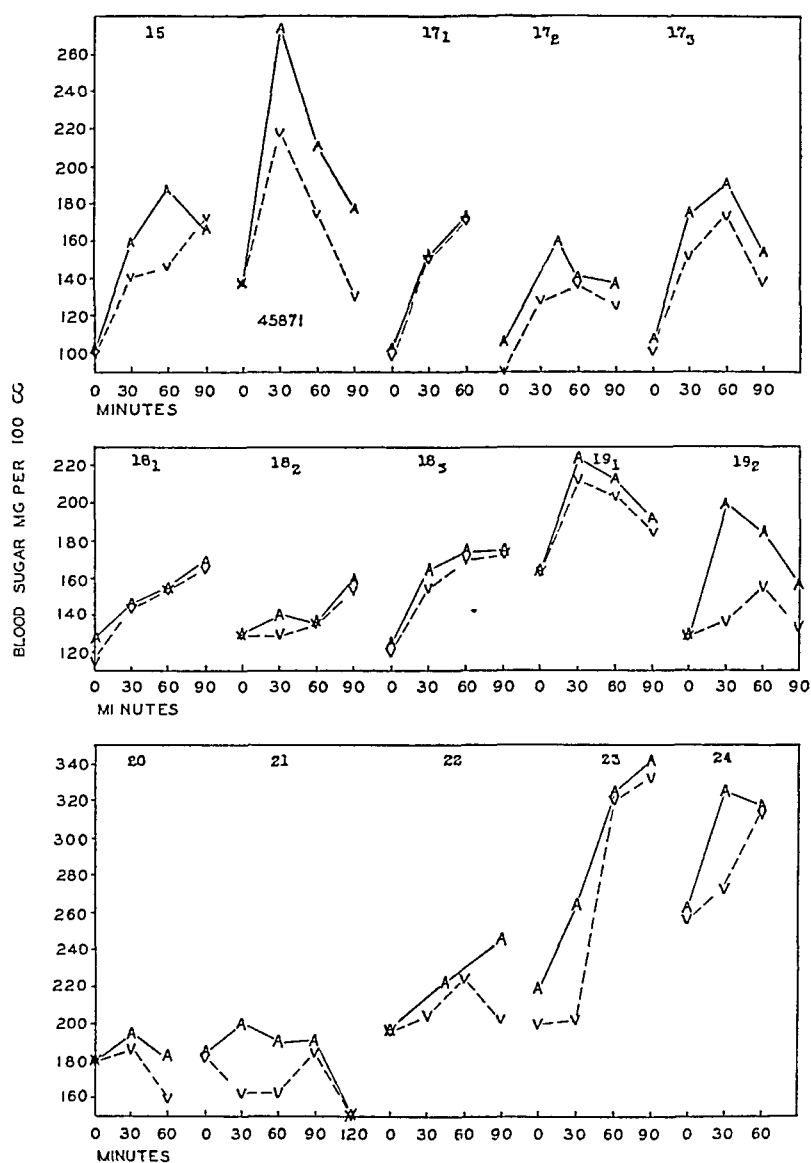


Chart 2—Blood sugar curves of diabetic patients. A—A and V—V represent cutaneous and venous blood sugar curves, respectively. The case numbers are given above the curves.

In mild diabetes, then, the ability of the tissues to remove sugar from the blood, as evidenced by the development of an arterial-venous difference after meals, is seldom abolished. It is usually apparent only at a higher blood sugar level than that required to produce it in the normal

person. If this were not the case, arterial-venous differences during fasting would be observed more often. In some instances, it seems to be more rapidly exhausted than normally. Even in the diabetic patient, it is impossible to determine renal thresholds or the degree or extent of hyperglycemic reactions from studies of the venous blood alone.

Table 1 illustrates the effects of insulin followed by a meal on the cutaneous and venous blood sugar of patients with diabetes of variable severity, but sufficiently grave to require treatment with insulin. The blood sugar measurements were taken at different intervals after doses of insulin and after breakfast. Both the insulin dosage and the meals were those which the patients were regularly receiving at the time of the observations on the blood sugar. In only one instance, case 27, did appreciable glycosuria result, and in no case did the blood sugar fall to hypoglycemic levels during the period of observation.

With the exception of case 28, the diets varied but little: carbohydrate from 33 to 51, protein from 19 to 23 and fat from 41 to 65 Gm. The insulin dosage, however, varied from 5 to 45 units. Although the doses, judged by their effects on glycosuria and glycemia, seemed to be well adjusted to the needs of the patients,<sup>13</sup> they bore no relation to the blood sugar level during fasting. This is only one illustration of the now well recognized fact that insulin dosage cannot be calculated in advance from either the blood sugar level or the diet, or both, but must depend on the nature of the disease in the given person.

Positive arterial-venous differences during fasting were encountered with far greater frequency in this group of patients than in normal persons, patients with borderline glycosurias or even mild cases of diabetes. Lawrence<sup>14</sup> reported similar results. This is strangely at variance with the generally accepted view that the most characteristic functional disturbance in diabetes is an impairment of the ability of the tissues to remove dextrose from the blood and utilize it. Such large arterial-venous differences can mean only that the tissues are actively absorbing sugar. If the figures are carefully analyzed, there seems to be a tendency for large differences to occur more frequently in patients with high blood sugar levels during fasting. This is clearly brought out by the figures compiled in table 2 from the studies of all the patients with diabetes.

From the data in table 2, one might infer that the diabetic patient has not lost the power of mobilizing dextrose into the tissues, but requires a higher concentration of sugar in the blood to activate the mechanism for the removal of dextrose. When the blood sugar rises

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13 Case 27 is an exception. On the day of the test, a rapidly spreading cellulitis developed in a gangrenous foot, necessitating a rapid increase of the insulin dosage.

14 Lawrence (footnote 3, fourth reference).

TABLE 1—*Effects of the Administration of Insulin Followed by a Meal in Patients with Diabetes*\*

Time, Minutes	Case 19			Case 22			Case 22		
	Arte- rial	Venous	Differ- ence	Arte- rial	Venous	Differ- ence	Arte- rial	Venous	Differ- ence
0	151	138	13	160	160	0	187	187	0
	Insulin, 10 units			Insulin, 20 units			Insulin, 20 units		
30	141	138	33	110	97	13	129	129	0
	Protein		23	Protein		20	Protein		19
	Fat		52	Fat		53	Fat		62
	Carbohydrate		33	Carbohydrate		41	Carbohydrate		51
60	148	142	6	82	72	10	135	128	7
90	133	128	5	74			120†	124	7
120	144	131	13				106	91	15
Urine sugar				Overnight		0	Overnight		0
				7-11 a m		0	7 11 a m		0
	Case 25			Case 26			Case 27		
0	161	119	42	195	195	0	177	174	3
	Insulin, 45 units			Insulin, 10 units			Insulin, 5 units		
30	131	126	5	169	169	0	177	184	-7
	Protein		22	Protein		20	Protein		22
	Fat		65	Fat		42	Fat		41
	Carbohydrate		41	Carbohydrate		33	Carbohydrate		34
60				217	186	31			
90	149	123	26				234	230	4
120	74	89	-15	205	180	25			
150							237	237	0
180	103	95	8				159	152	6
Urine sugar	Overnight		±	Overnight		0			
	7 11 a m		0	7-11 a m		0			
	Case 28			Case 29			Case 27		
0	195	190	5	209	183	26	227	211	16
	Insulin, 50 units			Insulin, 30 units			Insulin, 45 units		
30				200	185	15	216	229	-13
				Protein		23	Protein		21
				Fat		42	Fat		51
				Carbohydrate		33	Carbohydrate		33
60	151	134	17	211	150	61			
	Protein		23						
	Fat		100						
	Carbohydrate		100						
90							261	266	-5
120	125	121	4	147	111	36			
150							231	292	-11
180	103	95	8						
Urine sugar	Overnight		+	Overnight		0	Overnight, com- plete reduction		
	7 11 a m		0	7-11 a m		0	7 11 a m, com- plete reduction		
	Case 30			Case 31					
0	237	227	10	263	273	-10			
	Insulin, 20 units			Insulin, 15 units					
30	206	199	7	234	250	-16			
				Protein		20			
				Fat		42			
				Carbohydrate		33			
60	225	172	54						
	Protein		20						
	Fat		49						
	Carbohydrate		33						
90				283	238	45			
120	167	160	7	220	214	6			
150									
180	159	152	6						
Urine sugar	Overnight		0	Overnight		0			
	7-11 a m		±	7-11 a m		0			

\* Insulin was given immediately after the first estimation of blood sugar was taken (calculated in mg per hundred cubic centimeters), breakfast was given immediately after the thirty or sixty minute estimates of blood sugar, as indicated

† One hundred and five minutes

above this concentration, a positive arterial-venous difference appears whether the hyperglycemia follows the ingestion of food or develops during the fasting state. There are, of course, exceptions to the rule, for example, the patient in case 32, who had the highest observed hyperglycemia during fasting, exhibited a negative difference. One would expect such variability. In this case, the threshold for the activation of the mechanism for the removal of sugar may have been still higher.

A definite positive difference was established after doses of insulin and a meal in nine of eleven instances. In one no difference was observed and in another negative differences only. In only five experiments was a significant difference found after the administration of insulin alone. It cannot be inferred from this, however, that insulin failed to produce such a difference. In all but two experiments, breakfast was given thirty minutes after doses of insulin, in these two it

TABLE 2—*Study of Patients with Diabetes*

Number of Observations	Fasting Cutaneous Blood Sugar	Arterial-Venous Difference		
		Maximum	Minimum	Average
16	> 181	15	— 1	4
9	< 180	42	— 10	10
11	> 181		> 5	
5	> 181		< 4	
3	< 180		> 5	
6	< 180		< 4	

was withheld for an hour. In both the latter, cases 28 and 30, a large difference was produced at the sixty minute period. It seems not improbable that an interval of more than thirty minutes is required before the action of insulin becomes evident in the arterial-venous difference.

In spite of the fact that an arterial-venous difference became evident usually only after more than thirty minutes had elapsed, a distinct decrease in blood sugar was demonstrable almost invariably at the thirty minute point. This might be interpreted as an indication that the initial action of insulin is exerted on the liver and not on the tissues. Such a conclusion, however, must be accepted with caution. Undoubtedly, all the reactions involved in the disposal of carbohydrate are in mutual chemical and physiologic equilibrium. Changes in the system are only relative and not absolute. Diminution of the destruction of hepatic glycogen will have the same apparent effect, for example, as the increased formation of hepatic glycogen. It may be that insulin, by rendering carbohydrate available to the tissues, removes the stimulus which has in the diabetic patient led to hepatic glycogenolysis and the consequent production of hyperglycemia. It also accelerates the combustion



and storage of carbohydrate in the tissues. There may be, however, such a large excess of sugar available in these tissues that, for a time, it is unnecessary to draw on the store of blood sugar sufficiently to produce a perceptible arterial-venous difference.

Such an explanation would suffice for most of the experiments. At first sight it is hardly satisfactory in the instance of case 27, in which there was a continuously negative difference. On the day of the experiment, in this case, rapidly spreading cellulitis developed, attended by a sudden reduction of carbohydrate tolerance. Forty-five units of insulin, which had proved an adequate dose previously, was totally ineffectual in checking glycosuria on this day. The negative difference, then, is an expression of the absence of the effect of insulin. Under these circumstances, apparently, the tissues lose sugar to the blood, a phenomenon which, although contrary to physiologic conceptions of carbohydrate metabolism, has been noted in other connection in these studies.<sup>8</sup>

#### SUMMARY AND CONCLUSIONS

Arterial (cutaneous) and venous blood sugar curves have been studied after the administration of dextrose or mixed meals in patients with nondiabetic glycosuria and with diabetes, with and without insulin therapy.

The presence or absence of a positive arterial-venous blood sugar difference after meals cannot be used to distinguish benign glycosuria from diabetes.

In patients with benign glycosuria, the arterial-venous difference may be so great that the venous blood sugar, determined at thirty minute intervals, may never show hyperglycemia that is strikingly evident in the venous sugar curve. For the differentiation of types of benign glycosuria, venous sugar curves are of little value.

In mild diabetes, arterial-venous differences can usually be demonstrated at an abnormally high level.

After the administration of insulin, such differences develop at lower levels. Insulin, however, may lower the blood sugar level without causing an appreciable difference.

#### REPORT OF CASES

CASE 1—A girl, aged 4, was admitted to the hospital on Aug. 1, 1927, in June, 1927, her mother had noted slight polydipsia, and frequency of urination and glycosuria were discovered. One maternal aunt was known to have diabetes.

Physical examination revealed nothing of significance except adhesions of the labia minora and slight vaginal discharge, in which no gram-negative diplococci were found.

On diets containing 35 Gm. of protein, from 85 to 115 Gm. of fat and from 70 to 75 Gm. of carbohydrate, all samples of urine gave from  $\pm$  to 2+ reactions with Benedict's test and from  $\pm$  to + nitroprusside tests for acetone. Increasing

the diet to 250 Gm of carbohydrate had no apparent effect on the glycosuria. When from 5 to 10 units of insulin were given before breakfast, early morning samples continued to be from  $\pm$  to 2+, but the patient remained free from glycosuria throughout the day.

The blood sugar levels during fasting were: August 3, 70 mg per hundred cubic centimeters, August 11, 97 mg, August 31, 65 mg.

After being discharged from the hospital on September 1, the patient continued to show from  $\pm$  to + reactions with Benedict's test on a diet in which the carbohydrate was allowed to increase to 200 Gm or more. The glycosuria did not become greater, nor had diabetic symptoms appeared on this regimen by June, 1928. The dextrose tolerance test was made on Aug 16, 1927, but was not complete because difficulty was experienced in obtaining samples of venous blood.

The diagnosis was "borderline" glycosuria (diabetes?)

CASE 2—H. R., a boy, aged 12, first seen in the clinic on July 12, 1927, had been troubled for many years with attacks of hay-fever, during some of which a slight degree of glycosuria was noted. Diabetic symptoms never developed, but his mother restricted the carbohydrate of his diet, believing that this relieved the hay-fever. His father was mildly diabetic, and a maternal uncle, who proved to have hemochromatosis, had died in diabetic coma during an attack of lobar pneumonia.

TABLE 3—Results of Benedict's Test

	7 11 a m	11-4 p m	4 9 p m	9 7 a m
Feb 5 on an unlimited diet		4+	Complete reduction	4+
Feb 6, protein, 90 Gm, fat, 200 Gm, carbohydrate, 200 Gm	$\pm$	Complete reduction	4+	2+
Feb 7 protein, 90 Gm, fat, 200 Gm, carbohydrate, 200 Gm	Complete reduction	Complete reduction		

A dextrose tolerance test was made on February 7.

Physical examination gave essentially negative results.

On July 18, the blood sugar during fasting was 82 mg per hundred cubic centimeters. While on a diet estimated to contain 80 Gm of protein, 125 Gm of fat and 165 Gm of carbohydrate, urinalyses showed on July 17, at noon, Benedict's reaction, 0, 6 p m, +, 10 p m,  $\pm$ , July 18, 8 a m, 0.

A test for sugar tolerance was made on July 22. After this, the patient became and remained continuously aglycosuric on a diet containing 75 Gm of protein, 125 Gm of fat and 175 Gm of carbohydrate. In October, 1927, he was still aglycosuric, although he frequently overstepped his diet.

The impression was that the condition was benign glycosuria.

CASE 3—A youth, aged 19, a college student, in whom glycosuria had been discovered in September, 1926, on routine examination of the urine by the university health department, was admitted to the hospital on Feb 5, 1927. Weekly examinations showed that the glycosuria was persistent. It was not eliminated in a week, with the patient on a diet containing no obvious sweets nor starchy foods. The patient never had diabetic symptoms. One brother was under treatment for glycosuria.

Physical examination revealed no abnormalities.

The diagnosis was benign glycosuria (renal?)

CASE 4—A man, aged 37, a Jew, married, was admitted to the hospital on May 2, 1927, complaining of symptoms suggesting intermittent claudication except

that weakness was more evident than pain. No objective manifestations of neurologic or vascular disturbances were discovered.

When the patient was on a regular diet, glycosuria did not appear. A dextrose tolerance test was made on May 7 to determine whether the patient had the reduced carbohydrate tolerance usually found in thrombo-angitis obliterans.

The diagnosis was no disturbance of carbohydrate metabolism.

CASE 5—R W, a man, aged 36, first seen in the clinic in May, 1926, reported that nine years earlier, when he applied for insurance, examination disclosed a trace of sugar in the urine. This condition continued in spite of a moderate restriction of the diet.

A dextrose tolerance test was made on May 3, 1926.

On March 3, 1927, he returned to the clinic with glycosuria, but without diabetic symptoms, on an unrestricted diet.

After the ingestion of 100 Gm of dextrose, a dextrose tolerance test made by an insurance company on Jan 24, 1927, showed the results given in table 4.

The impression was that the condition was benign glycosuria (renal?).

CASE 6—A woman, aged 25, was admitted to the hospital for twenty-four hours on Sept 8, 1926, shortly after she had reported to the dispensary complaining of excessive menstrual pain. Glycosuria was discovered. She entered the hospital on Sept 8, 1926, for a dextrose tolerance test. After this time, she remained

TABLE 4—Results of Folin-Wu Test

Time	Venous Blood Sugar	Urine Sugar, per Cent
1 45 p m (fasting)	102	0 00
3 10 p m	130	0 75
3 45 p m	130	0 55

aglycosuric on a diet containing 70 Gm of protein, 175 Gm of fat and 150 Gm of carbohydrate. On Oct 29, 1927, an exploratory operation revealed that the left kidney was ectopic and lying in the pelvis. Appendectomy and hysteropexy were performed. While the patient was in the hospital on a regular diet, glycosuria did not appear. The blood sugar during fasting on admission was 87 mg per hundred centimeters.

The patient was not seen after being discharged from the hospital.

CASE 7—E V, a man, aged 42, was first seen in the clinic on May 18, 1928. Glycosuria had first been discovered in 1908, when the patient was operated on for hernia, and had been found at intervals ever since. He had been accepted, however, for service in the army in the Great War, at which time the urine was reported as normal. On two occasions, moderate dietetic restriction had affected the glycosuria but little. At no time had diabetic symptoms appeared.

During the winter of 1927 to 1928, he had been troubled with nervousness and exhaustion, especially marked before meals and relieved after the ingestion of food.

Physical examination gave essentially negative results. Urine passed in the clinic gave a 4+ Benedict reaction. A dextrose tolerance test was made on May 22.

Urinalyses showed May 23, before lunch, Benedict's,  $\pm$ , 4 p m, +, 7 p m, 3 +, 10 p m, +, May 24, 7 a m, +, 10 a m, 4 +.

With a restriction of the diet to 90 Gm of protein, 200 Gm of fat and 150 Gm of carbohydrate, variable, often considerable, amounts of sugar appeared in all samples.

The impression was that the condition was benign glycosuria (?).

CASE 8—A man, aged 54, was admitted to the hospital on March, 12, 1928. Glycosuria had been discovered in 1918, when he was suffering from a carbuncle on the nose. In the intervening ten years, no diabetic symptoms had appeared, although he had dieted only at intervals and had then omitted only obvious sweets and starches. In the six months before admission, on such a regimen, he had lost 9 pounds (4.1 Kg.)

Physical examination gave essentially negative results.

While he was in the hospital, from March 12 to 19, the urine never gave more than a  $\pm$  reaction with Benedict's solution. The diet, meanwhile, had been gradually increased from 60 Gm of protein, 150 Gm of fat and 125 Gm of carbohydrate, to 80 of protein, 175 of fat and 175 of carbohydrate, equally distributed in the three meals. On March 18, 25 Gm of dextrose was added to his breakfast without producing glycosuria.

A dextrose tolerance test was made on March 17.

The impression was that the condition was benign glycosuria.

CASE 9—F. B., a man, aged 24, a medical student, was first seen in the clinic on Feb. 14, 1927. In 1917, he was found to have glycosuria, which cleared up after one week of moderate restriction of the diet. Shortly after this, a dextrose tolerance test was done, on the basis of which he was told that he did not have diabetes. No further urinalyses were made until 1927, when repeated tests again revealed a slight degree of glycosuria. At no time did he have diabetic symptoms. His past history was unimportant. His father was said to have "benign glycosuria," and at one time one brother had been temporarily refused life insurance because of glycosuria.

With the patient on a full diet, examinations of the urine showed: February 17, before lunch, Benedict's test,  $+$ , before supper,  $2+$ , before bed,  $2+$ , on February 18, before breakfast,  $2+$ . No acetone was found in any of the samples.

On February 17, the blood sugar during fasting was 83 mg per hundred cubic centimeters.

A dextrose tolerance test was made on February 20. No subsequent examinations have been made.

The diagnosis was benign glycosuria.

CASE 10—A boy, aged 14, admitted to the hospital on Feb. 23, 1926, had fallen while skating on January 13. The fall dazed him, although he did not become unconscious. No fractures or lacerations were produced. On January 13, 14, 15 and 16, a slight degree of glycosuria was observed. Examination on January 19 and on February 1, however, revealed no sugar. On February 16, three hours after an ordinary breakfast, the blood sugar was 114 mg per hundred cubic centimeters by the Folin-Wu technic. He had no diabetic symptoms at any time and no other symptoms after the first twenty-four hours.

Physical examination gave entirely negative results.

A dextrose tolerance test was made on February 25.

The impression was that the condition was symptomatic glycosuria, associated with concussion of the brain.

CASE 11—A woman, aged 60, admitted to the hospital on Feb. 2, 1927, had been troubled with dizziness on exertion and polydipsia for one year. At the onset, she had transient glycosuria. One month before admission, polydipsia and polyuria had recurred, and sugar was again found in the urine. This condition again disappeared rapidly without treatment.

Physical examination revealed nothing of importance. For the first two days in the hospital, she had a slight febrile reaction. On February 3, the blood sugar

during fasting was 109 mg per hundred cubic centimeters. On a diet of 60 Gm of protein, 150 Gm of fat and 100 Gm of carbohydrate, the urine remained sugar-free continuously.

A sugar tolerance test was made on February 5, venous blood could not be obtained.

The impression was that the condition was early diabetes (?)

CASE 12—J H, a man, aged 38, was first seen in the clinic on Oct 1, 1926, six months after he had been found to have glycosuria in the course of an examination made when he applied for insurance. During this time it had been found at intervals. On April 25, 1926, the blood sugar during fasting was 115 mg per hundred cubic centimeters by the Folin-Wu method. From July 1 to October 1, he lived on a diet without sweets, potatoes and white bread. At no time had he developed diabetic symptoms. When dieting, but not before, he lost 8 pounds (3.6 Kg). One brother was known to have had transient glycosuria.

The physical examination gave essentially negative results.

On October 1, after a period of dieting, the urine was sugar-free. He then resumed a normal diet. A dextrose tolerance test was made on October 10. After this time, on a diet containing 65 Gm of protein, 150 Gm of fat and 200 Gm of carbohydrate, he remained aglycosuric even when he became careless and added

TABLE 5—*The Results After Fasting and the Ingestion of Insulin*

	Arterial	Venous	Difference
Fasting	89	93	—4
30 minutes after insulin	68	74	—6
60 minutes after insulin	54	50	4

small extra portions of bread and fruit. The patient has not returned since the fall of 1926.

The impression was that the condition was mild diabetes.

CASE 13—R N, a physician, aged 25, was apparently in excellent health. On several occasions, dextrose was discovered in the urine. He had never had diabetic symptoms. Physical examination revealed no abnormalities other than a general tendency to vasomotor instability.

The first two tolerance tests were made in the fall of 1925. The third test was made on May 8, 1927.

The effect of 10 units of insulin on the same subject was studied a few days later and was reported in a previous article.<sup>7</sup>

At this point, he developed symptoms of insulin shock and in the course of the next forty-five minutes was given 100 cc of orange juice, some dextrose and his regular breakfast. One hundred and twenty minutes after the ingestion of insulin, the arterial blood was 149 and the venous, 124, with a difference of 25.

CASE 14—G P, a woman, aged 65, with no symptoms of diabetes, had shown slight glycosuria at intervals for three months.

Physical examination revealed nothing important.

A carbohydrate tolerance test was made in April, 1926. During the succeeding two years, the patient lived on a normal diet without developing further glycosuria or any diabetic symptoms.

CASE 15—A man, aged 57, was admitted to the hospital on Oct 12, 1926, following a year of sleeplessness, blurring of vision and steady loss of weight. At the onset, he had slight polyuria and polydipsia. Repeated examinations of the urine had shown glycosuria on several occasions.

On September 14 and 21, when he was seen in the clinic, no sugar was found in the urine, and the physical examination was negative except for tachycardia, nervousness and evidence of loss of weight. On September 21, the blood sugar during fasting was 103 mg per hundred cubic centimeters.

On September 23, he was suddenly seized with an attack of vomiting and diarrhea, and his temperature rose to 102 F. The temperature subsided rapidly, but the diarrhea persisted.

At the time of admission, he appeared emaciated and chronically ill. Blood culture was sterile. From the stools, dysentery bacilli of the Hiss and Strong group were isolated. At first, he had leukopenia with low grade fever, which condition gradually cleared up. No sugar was found in the urine, although the diet was gradually increased to protein, 90 Gm, fat, 200 Gm, carbohydrate, 300 Gm, without insulin.

A tolerance test was made on October 31.

He was discharged on November 8.

CASE 16—A woman, aged 22, was admitted to the hospital on Sept 29, 1925, because of vomiting, apparently of psychoneurotic origin. On Nov 27, 1926, she was again admitted because of an incomplete abortion. The same cause brought her to the hospital on Nov 12, 1927. On the first two occasions, the urine, on several examinations, was free from sugar. At the time of the third admission, she had a moderate degree of glycosuria, polyuria and polydipsia. These conditions cleared up rapidly under dietetic treatment, and she was discharged on Dec 21, 1927, aglycosuric on a diet of protein, 60 Gm, fat, 125 Gm, and carbohydrate, 175 Gm, without insulin.

Blood sugar during fasting was November 17, 127 mg, November 19, 75 mg per hundred cubic centimeters.

A dextrose tolerance test was made on November 29.

CASE 17—A man, aged 45, admitted to the hospital on Sept 4, 1925, had been struck by an automobile, and sustained fractures of the tibia, fibula and radius. On admission, he appeared much shaken and somewhat shocked and had transient auricular fibrillation. Marked glycosuria was discovered which, at first, could be controlled only with 30 or 40 units of insulin on a diet of 80 Gm of protein, 150 Gm of fat and 125 Gm of carbohydrate. His tolerance rapidly increased so that he was finally kept aglycosuric without insulin on a diet of protein, 80 Gm, fat, 150 Gm, and carbohydrate, 300 Gm. Tolerance tests with the patient on this diet were made on October 10 and 13 and November 6.

He was discharged from the hospital on November 7.

CASE 18—A woman, aged 70, admitted to the hospital on Nov 27, 1925, gave a history of polydipsia, polyuria and occasional incontinence of urine of from six to ten years' duration, increasing in severity. In 1920, she broke the left hip, and since then had been able to walk only with the aid of crutches. At this time, glycosuria was discovered. On Nov 20, 1925, she slipped and fell, after this, frequency, incontinence and glycosuria grew worse and she became unable to walk.

On admission, she appeared emaciated and poorly cared for, presenting a crusted, desquamated, macerated area over the lower part of the back, and over the buttocks and the left thigh. She proved to have an ununited fracture of the neck of the left femur, slight cardiac decompensation and chronic cystitis, besides diabetes of moderate severity.

With nursing care, a restricted diet and administration of insulin, she improved rapidly. At first, 50 units of insulin was required to keep the urine sugar-free when she was on a diet of 60 Gm of protein, 150 Gm of fat and 100 Gm of carbo-

hydrate When she was discharged from the hospital on December 30, 30 units of insulin given daily before breakfast was sufficient with the same diet

Tolerance tests were made on December 3, 8 and 15 On these days, insulin was omitted before breakfast and given before lunch instead The diet, results of urinalyses and insulin dosage on these days are given in table 6

CASE 19—A man, aged 38, was first admitted to the hospital on April 20, 1922 In 1920, blurring of vision, polyuria and polydipsia developed suddenly, and he lost 85 pounds (38.6 Kg) in two months Glycosuria was discovered and a diet prescribed to which the patient did not adhere

In the hospital, his diet was gradually increased to protein, 60 Gm, fat, 150 Gm, and carbohydrate, 300 Gm, without the appearance of glycosuria After the ingestion of 75 Gm of dextrose on May 3, the venous blood sugar, tested by Benedict and Lewis' trinitrophenol method, rose to 262 mg per hundred cubic centimeters after two hours, and was still 136 mg at the end of three hours After two hours, the urine contained 2 per cent of sugar On April 21, the blood sugar during fasting was only 158 mg

On a diet of 100 Gm of protein, 200 Gm of fat and 200 Gm of carbohydrate, to which he did not adhere continuously, he remained aglycosuric until Nov 1, 1922, at which time he contracted a severe cold On November 22, he entered the

TABLE 6—*Diet, Urinalyses and Insulin Dosage*

Date	Diet			Urine, Benedict's Reaction				Insulin	
	Protein, Gm	Fat, Gm	Carbo- hydrate, Gm						
				A M 7-11	P M 11-4	P M 4-9	A M 9-7	Noon	P M
December 3	60	150	100	±	2+	0	0	30	10
December 8	60	150	100	0	2+	±	0	30	10
December 15	60	150	100	0	+	±	0	20	0

hospital where the urine became sugar-free only when the diet was reduced to 75 Gm of protein, 150 Gm of fat and 100 Gm of carbohydrate On November 23, the blood sugar during fasting was 231 mg After being discharged from the hospital, he was able to increase his diet gradually to its original value, where it was maintained (with the exception of a short period in January, 1923, when he had furunculosis) until November, 1925, when he was admitted to the hospital on account of an infected foot and a cold At this time, 10 units of insulin was required to keep the urine free from sugar on a diet of 75 Gm of protein, 200 Gm of fat and 125 Gm of carbohydrate On November 12, the blood sugar during fasting was 219 mg

Tolerance tests were made on November 13, 19 and 24, their results are shown in table 1 The diets and results of urinalysis on these dates are shown in table 7

After the patient was discharged from the hospital, the infection of the foot became worse and drainage was necessary For a time, the dosage of insulin had to be increased, however, as the condition of the foot cleared up, he was able to reduce the dosage to 5 units daily and, in December, 1927, to omit insulin entirely for a while, with a diet of protein, 75 Gm, fat, 200 Gm, and carbohydrate, 125 Gm

CASE 20—A woman, aged 74, admitted to the hospital on Oct 1, 1925, had been troubled for two months before with polyuria, polydipsia and some dysuria, which conditions improved with dietetic regulation In the last week of September, the left leg and foot became swollen

On admission, she had moderate edema of the left leg and foot and evidences of subacromial bursitis on the right side. The blood sugar during fasting was 212 mg per hundred cubic centimeters.

The diabetes was easily controlled without insulin, but with a diet of 60 Gm of protein, 100 Gm of fat and 125 Gm of carbohydrate. The condition of the shoulder improved rapidly, and the edema, which was apparently due to thrombosis of varicose veins, subsided.

A tolerance test was made on October 8.

She was discharged from the hospital on October 15.

CASE 21—A man, aged 42, was admitted to the hospital on April 15, 1927, six weeks after he noted general malaise, polyuria and polydipsia, with loss of weight. Ten days later he had vomited several times and, after that, rapidly lapsed into a semistuporous condition. Glycosuria had been discovered, and he had improved rapidly with insulin and dietary therapy. At first, 70 units of insulin was required daily, however, this dosage was rapidly reduced to 40 units. In the days preceding admission to the hospital, frequent insulin shocks had occurred.

Physical examination revealed nothing significant. It proved possible to eliminate insulin rapidly and to increase the diet to 75 Gm of protein, 200 Gm of fat and 150 Gm of carbohydrate.

TABLE 7—*Diet and Results of Urinalysis*

Date	Diet			Benedict's Test of Urine				Insulin		
	Protein, Gm	Fat, Gm	Carbohydrate, Gm					A M	Noon	P M
				A M 7-11	P M 11-7	P M 4-9	A M 9-7			
November 13	60	150	100	+	+	4+	Complete reduction		10	10
November 19	75	175	100	0	0	0	0	10	0	0
November 24	75	200	125	0	0	0	0	0	10	0

A tolerance test was made on April 30.

Blood sugar estimations during fasting were April 16, 129 mg, April 22, 123 mg, April 26, 123 mg.

He was discharged from the hospital on May 4.

He continued aglycosuric without insulin for six months. At the end of this time, following a cold, he had to resume the ingestion of 15 units of insulin before breakfast and 10 before supper.

CASE 22—A man, aged 30, was admitted to the hospital on Oct 26, 1925, three months after he had noticed increasing weakness and frequent headaches. About October 12, polyuria and polydipsia developed. During three months, he lost 20 pounds (9 Kg).

On admission, physical examination was essentially negative except for evidences of wasting and dehydration. The blood sugar during fasting was 172 mg per hundred cubic centimeters.

The diabetes was easily controlled with diet and insulin, and he was discharged on Nov 11, aglycosuric, on a diet of protein, 60 Gm, fat, 200 Gm, and carbohydrate, 150 Gm, with 20 units of insulin daily before breakfast.

He did not adhere to treatment and was readmitted on Sept 17, 1927, on the verge of coma. On this occasion, signs of pulmonary tuberculosis were discovered, and bacilli were found in the sputum.

The results of tolerance tests made on Oct 27 and Nov 3 and 10, 1925, are shown in table 1.



CASE 23—A woman, aged 40, was admitted to the hospital on Dec 1, 1927, one year after the development of intense genital pruritus. No glycosuria was found at that time. The pruritus was attended by frequency of urination and was not relieved by vaginal douches.

Physical examination revealed lacerations of the perineum. On admission, the urine showed a doubtful ( $\pm$ ) reaction to Benedict's reagent. On a diet of 60 Gm of protein, 150 Gm of fat and 150 Gm of carbohydrate the urine showed a complete reduction of Benedict's on one occasion after breakfast, other samples of urine contained smaller amounts of sugar.

A tolerance test was made on December 6.

She was discharged on December 9.

CASE 24—A woman, aged 42, was admitted to the hospital on Nov 14, 1927. Glycosuria had been discovered in 1918, however, no diabetic symptoms appeared, although no restriction of the diet was practiced. In March, 1926, a blister appeared on the right great toe, which did not heal until June. On Nov 11, 1927, she developed an infection of the right foot.

On admission, she presented a cellulitis of the right foot extending from an initial focus between the fourth and fifth toes. At the time of admission, the blood sugar during fasting was 170 mg per hundred cubic centimeters. The infection cleared rapidly, and the foot healed with nonoperative, conservative treatment.

At first, 10 units of insulin was required with a diet of 70 Gm of protein, 125 Gm of fat and 100 Gm of carbohydrate. Later, the use of insulin was eliminated, and the dosage of carbohydrate was increased to 125 Gm.

A tolerance test was made on November 28.

She was discharged on November 29.

CASE 25—A man, aged 25, admitted to the hospital on June 4, 1927, presented a typical picture of Friedreich's ataxia, which had developed in the course of the preceding five years. Three weeks before admission, polyuria and polydipsia appeared, and for a somewhat longer time he had been losing weight.

Except for wasting and the evidences of the Friedreich's ataxia, physical examination was essentially negative.

He proved to have a severe case of diabetes, and considerable difficulty was experienced in adjusting the dosage of insulin. After being discharged on July 30, he improved rapidly until September, at which time he was aglycosuric on a diet of protein, 60 Gm, fat, 200 Gm, and carbohydrate, 150 Gm, with 40 units of insulin before breakfast and 5 units before supper.

He was readmitted on Nov 5, 1927, in coma from carbon monoxide poisoning and remained in the hospital five days. On a diet of 60 Gm of protein, 200 Gm of fat and 125 Gm of carbohydrate he showed only traces of sugar in the urine at intervals, with 40 units of insulin before breakfast and 5 units before supper.

The results of a tolerance test, made on Nov 9, 1927, are shown in table 1.

CASE 26—A woman, aged 56, was admitted to the hospital at intervals, beginning in May, 1923. Glycosuria and diabetic symptoms were first noted in 1922. At the time of her first admission, she had slight hypertension, general arteriosclerosis and evidences of early senile dementia. The diabetes was mild, responding to moderate dietary restriction alone. Owing to her mental condition, however, it was impossible to control the glycosuria at home, and her family sent her to the hospital at intervals when her symptoms became distressing. On these occasions, insulin was used temporarily to eliminate glycosuria.

The results of a tolerance test, made on Oct 15, 1925, are shown in table 1.

On April 11, 1926, she suddenly became drowsy and weak, and weakness of the right side of the face and of the right hand developed, on April 24, a complete

ight hemiplegia developed, later complicated by bronchopneumonia. For a time, she required 45 units of insulin daily. As she improved, however, it was possible to reduce the dose to 10 units daily.

CASE 27—A man, aged 39, admitted to the hospital on Nov 20, 1927, had been troubled with polyuria for some years. Glycosuria had been discovered ten years earlier. On Nov 1, 1927, he hit the right ankle against a box. It became red, tender, painful and swollen. On November 6, similar swellings appeared in both thighs. On admission he presented a deep cellulitis of the right foot and ankle and two abscesses in the thighs. These were drained on November 21. On Nov 27, further incision of the ankle was necessary because the infection had involved the ankle joint and the adjoining bones. On December 6, pus was found in the urine. He gradually improved in spite of all these conditions until Feb 28, 1928, when the temperature suddenly rose and signs appeared in the lungs. He died on March 5. Blood cultures were repeatedly taken and always proved negative, although *Staphylococcus aureus* in pure culture was obtained from all the abscesses and from the urine.

The diabetes, under the influence of infections, proved to be severe.

The results of a tolerance test, made on Nov 23, 1927, are shown in table 1. On this day he received a diet of protein, 70 Gm, fat, 150 Gm, and carbohydrate, 132 Gm, with 45 units of insulin before breakfast, 20 before lunch, 40 before supper and 35 late in the evening. Nevertheless, all samples of urine throughout the twenty-four hours gave heavy reductions of Benedict's solution and moderate reactions for acetone. On the preceding and subsequent days, glycosuria was less marked when less insulin was given.

CASE 28—A woman, aged 64, was admitted to the hospital on Oct 16, 1924. A year earlier, because of polyuria and polydipsia she had consulted a physician who found glycosuria. She was placed on a diet and remained aglycosuric for six months. For four days before admission, the bowels did not move in spite of the administration of cathartics. At the time of admission, she appeared weak, emaciated and somewhat dehydrated. She had severe hemorrhoids and a rectum full of impacted feces. After the latter had been cleared out she was greatly relieved. She was discharged, aglycosuric, on a diet of protein, 50 Gm, fat, 200 Gm, and carbohydrate, 100 Gm, with 15 units of insulin daily before breakfast.

She was readmitted on Sept 13, 1927, with moderate acidosis, as the result of a seriously infected hand. This condition finally healed under treatment, and she was discharged on November 22, aglycosuric, on a diet of protein, 70 Gm, fat, 200 Gm and carbohydrate, 150 Gm, with 30 units of insulin before breakfast and 10 before supper.

The results of a tolerance test, made on Nov 8, 1927, are shown in table 1. At this time she was receiving a diet of protein, 70 Gm, fat, 300 Gm and carbohydrate, 300 Gm, with 50 units of insulin before breakfast and 20 units before supper, and was constantly aglycosuric.

CASE 29—A woman, aged 52, was admitted to the hospital on Nov 9, 1927. Six weeks earlier coryza had developed associated with slight infrascapular pain. Three weeks later, she had a similar cold attended by fever, cough and night sweats. She had no diabetic symptoms. On admission, she was found to have slight hypertension, and an acute pharyngitis due to hemolytic streptococci. Glycosuria was discovered.

She was discharged, aglycosuric, on a diet of 70 Gm of protein, 125 Gm of fat and 100 Gm of carbohydrate, with 30 units of insulin daily before breakfast.

After this, she was able to reduce the amount of insulin gradually to 16 units daily, by November

The results of a tolerance test, made on November 11, are shown in table 1

She was discharged on November 13

CASE 30—A woman, aged 60, was admitted to the hospital on Nov 16, 1927, and died on November 30. Permission for an autopsy was not obtained. Fifteen months earlier, she fell from a street car, sustaining an injury to the left shoulder which confined her to bed for three months and left a permanent disability. Glycosuria was discovered three months later, and was only partly eliminated by moderate dietary restriction. She also had polyuria and polydipsia, which persisted in spite of treatment. On November 11, she became drowsy and sleepy, and complained of dizziness, dyspnea and precordial pain on slight exertion.

At the time of admission, she appeared drowsy but irritable and not seriously ill, and she presented no abnormalities that could not be explained as the result of age and moderate arteriosclerosis. She complained of general pains and was unmanageable, at times refusing to eat. Her mental state was somewhat better from November 18 to 25, when she relapsed into her previous condition and refused all food. At the same time tachycardia developed. On November 29, she suddenly became stuporous and lost the use of the right arm and leg. She also became incontinent of urine and feces. That evening she lapsed into coma. The next day, signs of pneumonia appeared in the lungs, the temperature rose rapidly and she died.

The results of a tolerance test, made on November 23, are given in table 1. At this time, she was receiving a diet of protein, 70 Gm, fat, 150 Gm, and carbohydrate, 100 Gm, with 20 units of insulin before breakfast and 15 units before supper.

On November 21, the blood sugar during fasting was 340 mg per hundred cubic centimeters.

CASE 31—A woman, aged 49, admitted to the hospital on Sept 9, 1927, had noticed increasing fatigability and sleeplessness for two years. For three months, she had been troubled with dysuria and genital pruritus, and later with nocturnal and diurnal urinary frequency and axillary and submammary pruritus.

On admission, she appeared obese and presented an erythematous intertrigo in the axillae, under the breasts and about the genitalia, varicose veins of the legs, and slight edema of the ankles. The rash and itching disappeared rapidly under local and diabetic treatment. On admission, the blood sugar during fasting was 259 mg per hundred cubic centimeters, and 20 units of insulin was required to prevent glycosuria, with a diet of 60 Gm of protein, 100 Gm of fat and 100 Gm of carbohydrate. When she left the hospital, on Sept 23, only 5 units was needed to keep her aglycosuric, with a diet of protein, 70 Gm, fat, 75 Gm, and carbohydrate, 120 Gm. On November 21, the blood sugar during fasting was 192 mg.

The results of a tolerance test, made on November 15, are shown in table 1. On this day, the urine was sugar-free, and she was on a diet of protein, 52 Gm, fat, 95 Gm, and carbohydrate, 100 Gm, with 15 units of insulin before breakfast.

# AURICULAR FIBRILLATION

RESULTS OF SEVEN YEARS' EXPERIENCE WITH QUINIDINE SULPHATE  
THERAPY (1921 TO 1928)\*

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During the ten years following the introduction of quinidine<sup>1</sup> for the restoration of normal rhythm in cases of auricular fibrillation, ample opportunity has been afforded for the clinical and experimental study of this drug. To date more than 1,000 cases of permanent auricular fibrillation in which this treatment was used have been reported in the literature.<sup>2</sup> There can no longer be any doubt concerning the efficacy of quinidine in certain cases of absolute arrhythmia, its value in such cases justifies its continued use. We herein report a follow-up study of a series presented by one of us (P D W) five years ago,<sup>3</sup> and we also present a new series of cases collected since that time.

## OLD SERIES (1923)

In 1923, Viko, Marvin and White<sup>3</sup> reported seventy-one cases of nonparoxysmal auricular fibrillation and four cases of auricular flutter from the Massachusetts General Hospital and the New Haven Hospital. In 68 per cent of these patients the rhythm was restored to normal by quinidine, but in only 34 per cent was it maintained during the period of observation which varied from a few days (in the last case) to more than ten months. We present here the data obtained from a follow-up study of these patients. Three patients died apparently as a result of the quinidine therapy. To the present time (August, 1928) at least twenty-two more patients have died, but not from the quinidine therapy, so that at least one third of the entire group has died. Normal rhythm had been restored in sixteen of these twenty-two patients, in six the duration of normal rhythm was only from a few hours to days, so that quinidine therapy was undoubtedly without influence on the final outcome. Three of these six patients died of infec-

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<sup>1</sup> From the Massachusetts General Hospital

1 Frey, W. Ueber Vorhofflimmern beim Menschen und seine Beseitigung durch Chinidin, *Berl klin Wchnschr* **55** 450, 1918

2 Eismayer, G. Die Behandlung Unregelmässiger Herzthätigkeit mit Chinidin, *Deutsches Arch f klin Med* **156** 182, 1927

3 Viko, L E, Marvin, H M, and White, P D. A Clinical Report on the Use of Quinidine Sulphate, *Arch Int Med* **31** 345 (March) 1923

tions (miliary tuberculosis, bronchopneumonia and a streptococcus infection), one patient died from congestive failure a number of days after the course of quinidine therapy, one died two months later and one died five and a half years later. In three of the remaining ten patients the duration of normal rhythm was unknown, one of these died from bronchopneumonia and cardiac failure, eight months after quinidine therapy was used, one died three years later from heart disease and one died four years later. One patient who maintained normal rhythm for six and a half months died six and a half years later, one patient maintained normal rhythm for more than four months and died suddenly four years later, and two other patients, who maintained normal rhythm for thirteen and eleven months, respectively, died four years and two years later, respectively. Thus only three of the patients who died maintained normal rhythm until the time of death, the duration in these cases being six months, one and a half years (death from congestive failure) and three years (death from probable coronary thrombosis), respectively.

In the group in which normal rhythm was not restored, the duration of life after quinidine therapy for the remaining six patients who died was two months in two patients, three months in one, five and a half years in one and an unknown period in two.

We have been able to obtain follow-up data on thirteen other patients, all of whom are living, so that our observations are complete in thirty-eight cases, or over half of the entire series. Two patients have had uninterrupted normal rhythm for six and seven years, respectively, a third patient has had normal rhythm for six years, interrupted by one short paroxysm of auricular fibrillation, a fourth patient, after six years of normal rhythm, had a relapse of auricular fibrillation uninfluenced by quinidine therapy, a fifth patient, who was observed for only three years, maintained normal rhythm except for one or two readily controlled paroxysms, and a sixth patient, who has maintained normal rhythm for seven years, has a daily paroxysm of auricular flutter (?). The last mentioned patient prefers a paroxysmal to a constant arrhythmia. Thus, normal rhythm has persisted for from six to seven years (for three years in one patient who was then lost track of) in 11.7 per cent of the patients who responded to quinidine therapy, or in 23.1 per cent of those who did not have a relapse within the first ten months after the restoration of normal rhythm. It may be said, therefore, that in a small, but not insignificant group, the restoration of normal rhythm by means of quinidine sulphate is permanent (to date). We have observed two other patients, not included in this or the present report, who have maintained normal rhythm from the time it was restored until death, two and four years later, respectively.

Two of the seven remaining patients, five of whom had normal rhythm for a number of hours or days, are distinctly limited in their activity as a result of heart disease, and the remaining five are in fair health, though they are not symptomless and are living a restricted life.

The health of the group of patients who maintained normal rhythm is definitely better than that of the group in which normal rhythm was not restored or in which auricular fibrillation recurred within a short time. Five patients, including two patients who did not belong to this series, maintained normal rhythm until death, the duration of life being six months, one and a half years, two years, three years and four years, respectively. The duration of life in six unsuccessfully treated patients was two months in two patients, three months in one, five and a half years in one and an unknown period in two. Four other patients in whom normal rhythm was maintained for four months, six and a half months, eleven months and thirteen months, respectively, lived for four, six and a half, two and four years, respectively. Six patients in whom normal rhythm lasted only a few hours or days died soon after the quinidine therapy. Duration of life is therefore definitely longer in patients who maintain normal rhythm for six months or longer than in those who quickly revert to fibrillation or do not attain a normal rhythm. There is, however, no clear indication that life is prolonged by the resumption and maintenance of normal rhythm.

#### NEW SERIES OF CASES (1923-1928)

The new cases of nonparoxysmal auricular fibrillation and auricular flutter reported in this paper were seen at the Massachusetts General Hospital and in private practice during the past five years. This group consists of patients seen since the first report was made, and therefore is composed of new patients, with the exception of one or two who reentered the hospital on account of a relapse of auricular fibrillation. The total number of seventy cases comprises sixty-two of fibrillation and eight of flutter. Of the sixty-two patients with auricular fibrillation who were treated with quinidine sulphate, normal rhythm was restored in forty-two, or 67.7 per cent, of the eight cases of flutter, four patients, or 50 per cent, were successfully treated. Of the entire group, therefore, circus movement was abolished in forty-six, or 65.7 per cent, in comparison with 68 per cent of seventy-five cases reported in 1923 from the Massachusetts General Hospital and the New Haven Hospital,<sup>3</sup> and with 58.5 per cent of 1,058 cases collected by Eismayer in 1927.<sup>2</sup>

To date seventeen patients, or 24.3 per cent of the entire series of new cases, have died, eleven of these had had normal rhythm restored. Slightly less than one fourth, therefore, of the patients successfully treated with quinidine sulphate have already died. One patient died from bronchopneumonia shortly after the restoration of normal rhythm,

one died during the course of quinidine therapy shortly after the recurrence of auricular fibrillation, one from congestive failure soon after the restoration of normal rhythm, one during an unsuccessful course of quinidine therapy after two successful courses, and one following an operation, six days after the recurrence of auricular fibrillation. Four other patients died one month, seven months, eight months and one year, respectively, after the resumption of normal rhythm, but the duration of the normal rhythm is unknown. The tenth patient maintained normal rhythm for three years, when auricular fibrillation recurred at about the time of onset of subacute bacterial endocarditis. The duration of life in the eleventh patient is unknown.

In four of the six patients in whom normal rhythm had not been restored before death, the duration of life after the course of quinidine therapy was seven months, eight months, eleven months and two years, respectively, two patients died while still in the hospital.

Death occurred in 23.8 per cent of the patients in whom normal rhythm was restored and in 23.1 per cent of those in whom normal rhythm was not restored.

Thirty-five patients in whom normal rhythm was restored are living. Auricular fibrillation recurred in four patients from a few hours to one or two weeks. Four patients left the hospital with a normal rhythm, but have not been seen again. Six patients maintained normal rhythm for one month, five months, six months, eight months, fourteen months and four years, respectively, before experiencing a recurrence of the auricular fibrillation. In the remaining twenty-one patients, normal rhythm was maintained until the time of the last examination, that is, for four months or less in five patients, and in the remaining patients, for five months, eight months, ten months (two patients), eleven months, thirteen months, twenty-one months, twenty-two months, two years (in three patients), three years, three and a half years, and four years (two patients), respectively. The health of the patients in this group as a whole is good. One patient is troubled considerably by paroxysmal auricular fibrillation, another patient has paroxysms from two to three times a year, readily controlled by quinidine, and a third patient suffered from paroxysms for the first two and a half years after the restoration of normal rhythm, but for the past year and a half has been free from attacks.

Twenty-four cases in this series have been classed as failures, but in two of these the patients had previously had a restoration of normal rhythm while under treatment with quinidine, while a third patient was subsequently successfully treated and has now maintained a normal heart rhythm for five years interrupted by occasional short attacks of auricular fibrillation. One patient, in spite of unsuccessful quinidine and digitalis therapy, reverted spontaneously to normal rhythm five

years after the onset of auricular flutter. Follow-up data have been obtained in six of the remaining fifteen patients in this group who are living. Two were fairly well from two to three months later, one patient wrote that she had been in poor health for two and a half years, but that after an operation for gastric ulcer she was much better, one patient, a year and a half after discharge from the hospital, wrote that he was in poor health, a fifth patient is in good health two years later, although troubled by gallstones, and the sixth patient is in fair health one and a half years after leaving the hospital.

One of the patients who temporarily regained a normal heart rhythm is in good health, four and a half years later, and one has required institutional care since leaving the hospital two years ago.

During a period of observation of four years in the oldest cases, a normal rhythm has been maintained in 30 per cent of the entire series. This result is actually much better than that obtained in the original series, for although 34 per cent of the patients maintained normal rhythm at the time that the report was made, the oldest cases were observed during a period of only ten months. Our follow-up studies indicate definitely that much more satisfactory results have been obtained in the present series. The evidence in both series indicates that the health of the patients successfully treated is better than that of those unsuccessfully treated but that there is no essential difference in mortality or in duration of life.

The criteria used in the selection of cases for quinidine therapy were safety, the probability of success and the likelihood of benefiting the patient by terminating the abnormal rhythm. Patients with marked mitral stenosis or with congestive failure not readily responding to rest and digitalis were excluded. Quinidine therapy was not used in a number of suitable cases, as it was felt that the patient had nothing to gain by converting fibrillation to a normal rhythm. With the exception of two or three cases in which it was hoped that restoration of normal rhythm might avert a fatal outcome the condition of each patient was satisfactory when quinidine therapy was begun. Most of the patients were completely digitalized as a preliminary measure, even though there was no congestive failure. The usual though not invariable routine, after the customary test doses were given, was to administer 6 grains (0.38 Gm.) every two hours, five times a day, until normal rhythm was restored or toxic symptoms occurred. If this procedure was unsuccessful after from five to seven days, the drug was discontinued. All the patients received daily rations of from 3 to 9 grains (0.19 to 0.58 Gm.) after the restoration of normal rhythm for as long a time as they remained in the hospital. They were instructed to continue taking the drug at home for a few weeks and then, if possible, to get on without it.



That large doses of quinidine may usually be administered with impunity, even to patients with grave conditions of the heart, cannot be denied <sup>4</sup> It is equally certain that quinidine is a powerful drug, and that undesirable and even fatal events may occur from its toxic action, apart from the results of embolism It is reasonable to assert, therefore, that large doses should be avoided if possible If patients are properly selected for treatment, success is usually attained with surprisingly small amounts of the drug Nor is proper selection of cases alone necessary On the basis of clinical observations it appears that predigitalization, contrary to the opinion of some writers, allows the termination of circus movement with smaller doses of quinidine than would otherwise be required It has been noted, in reviewing the literature, that the method occasionally or frequently practiced in administering quinidine is not the most efficient The electrocardiographic <sup>5</sup> and pharmacologic evidence <sup>6</sup> available clearly indicates that the drug should be administered at least every two hours to obtain the best results

In the present group, in which the percentage of successfully treated patients compares favorably with all the published series, thirty-six patients received less than 100 grains (6.48 Gm) of quinidine, and only eight required more than 100 grains of the drug before the abnormal rhythm was terminated In two cases, the amount of quinidine taken is not known In twenty-eight patients, 50 grains (3.24 Gm) or less of quinidine was all that was needed to restore normal rhythm

The number of days of treatment with quinidine in the successful group was three or less in thirty-three cases, two in nineteen cases, one in five cases and more than seven in only two patients

#### FACTORS INFLUENCING THE RESPONSE TO QUINIDINE THERAPY

*Sex*—The group includes forty male patients in whom normal rhythm was restored in twenty-eight or 70 per cent, and thirty females, of whom 60 per cent were successfully treated It seems unlikely that sex is of any importance in determining or influencing the outcome of treatment, in spite of the disparity of the two groups

*Age*—In studying the distribution of successes and failures according to age, it was found impracticable to divide the cases into decades,

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4 Levine, S. A., and Stevens, W. B. The Therapeutic Value of Quinidin Sulphate in Coronary Thrombosis Complicated by Ventricular Tachycardia, *Am Heart J* **3** 253, 1928. Sidel, N., and Dorwart, F. G. Quinidin Sulphate in Auricular Fibrillation, *Boston M. & S. J* **196** 216, 1927.

5 Lewis, T. Wedd, A. M., Drury, A. N., and Iliescu, C. C. Observations upon the Action of Certain Drugs upon Fibrillation of the Auricles, *Heart* **9** 207, 1922.

6 Weiss, S., and Thatcher, R. A. Studies on Quinidin, *J Pharmacol. & Exper Therap* **30** 335, 1927.

as this resulted in groups too small to be of any value. We, therefore, made the division into two groups, one comprising all the patients from 10 to 40 years of age, and the other all the patients from 41 to 70 years of age. (A more detailed analysis of the factor of age has been made without, however, altering the conclusions.) In the group of younger patients (twenty-two), 81.8 per cent were treated successfully whereas in the group of older patients (forty-eight), normal rhythm was restored in only 58.3 per cent. This difference is striking and will be discussed in greater detail subsequently.

*Congestive Failure*—It has been stated by others that congestive failure influences adversely the result of treatment with quinidine sulphate and may be responsible for the variety of responses seen in the different age or etiologic groups. To exclude this factor, it is an easy matter to revise our figures by removing from the two large age

TABLE 1—*The Entire Series of Cases Divided Into Etiologic Groups*

Etiology	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Rheumatic	16	8	66.7
Hypertensive	3	0	100
Arteriosclerotic	10	6	62.5
Hypertensive and arteriosclerotic	3	6	33.3
Hypertensive and rheumatic	1	0	100
Hyperthyroid	3	2	60
Hyperthyroid and rheumatic	1	0	100
"Normal"	7	0	100
Doubtful etiology	2	2	50
Total	46	24	65.7

groups the twenty-three cases in which the condition was complicated by the presence of congestive failure at the time of admission to the hospital. Then there are fifteen cases in the younger group with restoration of normal rhythm in 93.3 per cent, and thirty-two cases in the older group, with restoration of normal rhythm in 65.6 per cent. Using these figures as a criterion, it is doubtful whether congestive failure influences the distribution of failures and successes in the various age groups to any important degree, although it may be a slight factor.

*Etiology*—Table 1 shows the division of the entire series into the various etiologic groups, together with the number of cases in each group and the results obtained.

It seems reasonable, for the purpose of statistical study, to combine the second, third and fourth groups in table 1 under the one etiologic heading, "hypertensive and arteriosclerotic," and to exclude the four cases of doubtful etiology, the case of a hypertensive and rheumatic heart and the case of a hyperthyroid condition and a rheumatic heart

Table 2 shows this revision and also the result of simplifying still further the two largest etiologic groups by removing the factor of congestive failure, the data for all patients who presented evidence of this complication were excluded in the second half of the table

It is of interest to consider the possible influence of age on the outcome of treatment in each etiologic group Table 3 has been constructed with this end in view

TABLE 2—*Revised Classification of Cases into Etiologic Groups*\*

Etiology	Entire Series			Restricted Series		
	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Rheumatic	16	8	66.7	11	5	68.8
Hypertensive and arteriosclerotic	16	12	57.1	12	5	70.6
Hyperthyroid	3	2	60			
Normal	7	0	100			

\* The four cases of doubtful etiology, the one in which there was a hypertensive and rheumatic condition of the heart and the one in which there was hyperthyroidism and a rheumatic condition of the heart have been excluded. In the restricted series in this and the following table, the cases in which there was congestive failure have been excluded

TABLE 3—*Etiologic Groups Divided According to the Age of the Patients*

Etiologic Group	Entire Series						Restricted Series					
	Ages from 10 to 40 Years			Ages from 41 to 70 Years			Ages from 10 to 40 Years			Ages from 41 to 70 Years		
	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Rheumatic	12	3	80	1	5	44.4	9	1	90	3	3	50.0
Hypertensive and arteriosclerotic	1	0	100	15	12	55.5	1	0	100	11	5	68.7
Hyperthyroid	0	0		3	2	60						
Normal	4	0	100	3	0	100						

Tables 1, 2 and 3 indicate a significant variation in response to quinidine therapy in the different age and etiologic groups. The exact rôle played by etiology and age cannot, however, be conclusively demonstrated from these figures alone. On account of the natural distribution of the diseases under discussion, the younger group contains most of the cases of rheumatic heart disease while the older group contains all but one of the cases of a hypertensive and arteriosclerotic condition of the heart. Table 3 indicates that age is of importance in the group

with rheumatic heart disease, but table 4, so far as one may draw conclusions from small groups, affords little or no evidence that age is a significant factor in this etiologic group. It becomes apparent that the striking difference between the two age groups in the response to quinidine therapy is related to the presence in the younger group of almost two thirds of all the cases of rheumatic heart disease, comprising over 68 per cent of the younger group. It is possible that age, so far as it has a bearing on the duration of heart disease, may be a factor of importance only in the cases of rheumatic disease with mitral stenosis, that is, the duration of mitral obstruction may be directly related to the degree of auricular damage, the extent of which might hinder the restoration of normal rhythm.

TABLE 4—*Cases of Hypertensive and Arteriosclerotic Heart Disease Grouped According to Age*

Years	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
30 to 40	1	0	100
41 to 50	3	2	60
51 to 60	6	5	55
61 to 70	6	5	55

TABLE 5—*Classification of Cases as to Age and Duration of Fibrillation*

Age Group	Less Than One Month			More Than One Month		
	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
10 to 40	10	2	83.3	4	2	66.7
41 to 70	7	2	77.7	17	18	48.6

There is some evidence that etiology has a minor influence on the response to quinidine therapy. All the cases of hyperthyroidism were in patients more than 40 years of age, and the response in this group was essentially the same as in the group with hypertensive and arteriosclerotic heart disease. The possibility is suggested, therefore, that the poor results in these two groups and in the older group of patients with rheumatic disease of the heart may be due, not to the age factor, but to the associated vascular changes that may occur with advancing age. In a normal heart, uniformly good results are obtained, irrespective of the age of the patient and of the duration of the fibrillation.

In the following paragraphs, evidence is presented to show the important influence of the duration of fibrillation on the response to

quinidine therapy, it is shown that this influence is independent of age and etiology. To determine if the factor of the duration of fibrillation is responsible for the apparent influence of age and etiology we have constructed tables 5 and 6 (in table 5 the data for the seven patients with normal hearts have been excluded). The conclusions already reached regarding these two factors are corroborated by the data in these tables and in table 10, that is, the etiology is of minor importance, whereas age is an important factor in the rheumatic group.

*Duration of Fibrillation*—The duration of fibrillation at the time that quinidine therapy is started appears to exert considerable influence

TABLE 6—*Cases of Rheumatic Heart Disease, Classified as to Age and Duration of Fibrillation*

Duration of Fibrillation	Ages from 10 to 40 Years			Ages from 41 to 70 Years		
	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Less than one month	8	1	88.9	1	1	50
More than one month	4	2	66.7	3	4	42.8

TABLE 7—*Entire Series of Cases Grouped According to the Duration of Fibrillation*

Duration of Fibrillation	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Less than one month	18	4	81.8
1 to 6 months	15	11	57.7
6 months to 1 year	5	4	55.5
1 to 2 years	3	2	60
2 to 3 years	0	2	0
3 to 4 years	1	0	100
5 to 10 years	1	1	50
Over 10 years	2	0	100
Questionable	1	0	100

on the outcome of treatment, as may be seen from tables 7 and 8. The patients with fibrillation of recent origin show the best response, as in 90 per cent of these the arrhythmia is terminated. In all cases of more than one month's duration, irrespective of the number of months or years of fibrillation, there is an equal propensity for normal rhythm to be restored when the patient is treated with quinidine, in some of our most strikingly successful cases, the patients had had auricular fibrillation for more than ten years.

We may conclude, then, that the duration of fibrillation is to a limited extent a decisive factor in the outcome of treatment. If the cases are divided into the two age groups already mentioned, it becomes

clear that age can be excluded as a factor in varying the response to treatment in any group formed on the basis of the duration of fibrillation

The discrepancy seen in the cases with fibrillation of over six months' duration depends on the presence, in this group, of five of the seven patients with normal hearts, four of whom fall in the age group of from 10 to 40 years. In addition, of the failures in this group one patient was almost moribund when quinidine was first given, and three other patients received inadequate amounts of the drug

If the group is still further analyzed to determine whether an etiologic factor may explain the variation in response apparently related

TABLE 8—Duration of Fibrillation in Patients with and without Congestive Failure

Duration of Fibrillation	Entire Series			Restricted Series,
	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Percentage in Which Normal Rhythm Was Restored
Less than one month	18	4	81.8	93.3
More than one month	27	20	57.4	64.5

TABLE 9—Grouping of Cases as to Duration of Fibrillation and Age

Duration of Fibrillation	Ages from 10 to 40 Years			Ages from 41 to 70 Years		
	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Less than 1 month	10	2	83.3	8	2	80
1 month to 6 months	2	2	50.0	11	9	55
6 months to 1 year	2	0	100.0	5	4	55.5
Over 1 year	4	0	100.0	3	5	37.5

to the duration of fibrillation, the results obtained are striking—although we are now dealing with small figures—and indicate that etiology may be excluded as a factor in estimating the influence of the duration of fibrillation on the response to quinidine therapy (table 10)

*Condition of the Patient*—The condition of the patient, as estimated by the presence of objective signs of congestive failure, the general clinical impression and the ventricular rate when quinidine therapy is started (the latter, however, is closely related to digitalization), is of some importance in its influence on the success or failure of treatment. Of twenty-three patients presenting evidence of congestive failure on entrance to the hospital, normal rhythm was restored in only 47.8 per cent, while of forty-five patients without this complication, normal rhythm was restored in 73.3 per cent. However, nine of the eleven patients in whom normal rhythm was restored had marked

failure, while only five of the twelve whose rhythm was not restored to normal presented evidence of considerable failure. In this group of patients with congestive failure, in only 57.1 per cent of the seven cases with fibrillation of less than one month's duration was rhythm restored to normal, of the sixteen with fibrillation of over one month's duration, rhythm was restored to normal in 77.7 per cent.

Three of the eleven patients of this group in whom quinidine terminated circus movement died, one following an operation, one from progressive congestive failure (normal rhythm was maintained to the end) and one from bronchopneumonia. Quinidine can be definitely excluded as a cause of death in these cases.

One of the twelve patients in whom normal rhythm was not restored died from pneumonia and one died from congestive failure.

In this entire group of twenty-three patients with congestive failure, with the exception of two patients who died, the condition of the patients,

TABLE 10—*Grouping of Cases According to Duration of Fibrillation and Etiology*

Duration of Fibrillation	Rheumatic			Hypertensive and Arteriosclerotic		
	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Less than one month	9	2	81.8	5	1	83.3
Over one month	7	6	53.8	11	11	50

as the result of rest and digitalization, was satisfactory when quinidine therapy was started.

*Size of the Heart*—In ten patients without any cardiac enlargement the rhythm was restored to normal in all, this group including, of course, the seven patients with apparently normal hearts. The rhythm was restored to normal in forty patients, 57.5 per cent, with from slight to moderate enlargement, and in nineteen patients, 63.1 per cent, with marked enlargement. The relative size of the heart when it is enlarged, therefore, seems to bear no relation to response to quinidine therapy.

A past history of decompensation and the type of fibrillation as seen in the electrocardiogram (fine or coarse) have no influence on the outcome of treatment. Rhythm was restored to normal in 67.8 per cent of twenty-eight patients whose electrocardiograms showed the fine type of fibrillation, while it was restored to normal in 71.4 per cent of twenty-eight patients with a coarse type of fibrillation.

*Ventricular Rate*—The ventricular rate when quinidine is started is apparently of some importance as may be seen from table 11. The ventricular rate, however, is largely influenced by digitalization in these

cases, the figures in tables 12 and 13 suggest the beneficial action of digitalization in favoring the response to quinidine. Three patients received no digitalis while in the hospital, but the nature of the T wave of the electrocardiogram indicated probable digitalization before entrance. The data for these cases are not included in the table.

In studying the effect of digitalis on the rate of circus movement, Lewis<sup>5</sup> and his co-workers found that constant results were obtained only when the drug was given in full therapeutic doses. The only patient in whom a fall in rate of circus movement was observed was

TABLE 11—*Cases Grouped According to Ventricular Rate When Quinidine Therapy Began*

Ventricular Rate	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Less than 80	25	11	69.4
80 to 90	5	5	50
90 to 100	2	4	33.3
More than 100	4	4	50

TABLE 12—*Cases Grouped According to the Degree of Digitalization*

Digitalization	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Complete	36	18	66.7
Insufficient	2	3	40
None	5	3	62.5

TABLE 13—*Cases Grouped According to Degree of Digitalization*

Digitalization	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Complete	36	18	66.7
None or insufficient	7	6	53.8

receiving only small doses of digitalis. We have, therefore, in table 13, combined the two groups—those in which the patients received no digitalis and those in which an insufficient amount was given. It is evident that the response is better in patients who have been fully digitalized.

*Miscellaneous Factors*—In studying the cases we have attempted, in each instance, to explain a failure. By doing so, we have been able in a large measure to account for many of the unsuccessful cases. Probable causes, at least, may be assigned, but one can never state with finality, on clinical grounds alone, the ultimate cause of failure. Such a



study has merely emphasized that certain conditions may interfere with the desired action of the drug

The entire group of failures includes twenty-six cases of permanent fibrillation and flutter. It is interesting that in nine of these twenty-six cases the patients received strikingly small doses of quinidine, on account of the development of toxic symptoms, or because of refusal to accept the treatment as prescribed, or for no good reason at all. It is fair to assume that in at least a few of these patients, the fibrillation would have been converted to normal rhythm with adequate doses of quinidine. Four other patients had auricular flutter, and it has been our experience, as well as that of others, that quinidine is not so effective in this condition as is digitalis. Study of these four cases reveals additional possible reasons for the undesirable outcome. One patient entered with extreme congestive failure and hyperpyrexia, and soon died. This patient, furthermore, received only 36 grains (2.33 Gm.) of quinidine in two days. A second patient had severe heart disease with considerable enlargement and crippling angina pectoris. A third patient was given no digitalis. The case of the fourth patient is remarkable in that after five years of persistent flutter, the paroxysm ended spontaneously.<sup>7</sup> Two patients with auricular fibrillation were inveterate drinkers of alcoholic beverages, and since we have repeatedly observed that alcohol may apparently precipitate auricular fibrillation, we therefore suggest the possibility that this fact may have interfered with quinidine therapy. In addition, one of these patients received inadequate doses of quinidine. In three other patients, an intercurrent infection complicated the situation, in one patient, a severe, fatal pneumonia. Two of these three patients were in poor condition when the quinidine therapy was started, and one patient was incompletely digitalized.

We may conclude, then, that in addition to factors already discussed, failure to restore normal rhythm in our series depended on inadequate amounts of quinidine, intercurrent infection and possibly alcoholism. As a rule, more than one factor was present in a given case, accentuating the probability of failure. Grossly inadequate dosage of quinidine was the most frequent cause, being present in more than one third of the failures.

#### THE USE OF DIGITALIS WITH QUINIDINE

The use of digitalis with quinidine in the treatment of patients with auricular fibrillation has not been sanctioned by all who have studied this problem. In the literature the views expressed vary from a recom-

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<sup>7</sup> Sprague, H. B., and White, P. D. Auricular Flutter, *J. A. M. A.* 90:1772 (June 2) 1928.

mendation of its use to a declaration that it is contraindicated because of the combined toxic effects of the two drugs

Cantani,<sup>8</sup> in a publication of 1905, is given credit for the opinion that quinidine exerts a favorable influence on the action of digitalis Schott,<sup>9</sup> in 1920, advised against the combined administration of quinidine and digitalis, on the grounds that a high degree of A-V block was thus produced in guinea-pigs. In repeating these experiments, Korns<sup>10</sup> came to the conclusion that asphyxia, produced by the action of quinidine on the respiration, was responsible for these high grades of A-V block, and that if the precaution were taken to exclude this factor, one never observed a block of a higher grade than 2:1. According to Korns, asphyxia alone is capable of producing all grades of A-V block in guinea-pigs, including complete dissociation. Frey, in his second publication on the use of quinidine,<sup>11</sup> advocated digitalization in cases of congestive failure, but, in a later publication,<sup>12</sup> was of the opinion that the combined use of digitalis and quinidine was not advisable. In a previous publication<sup>3</sup> on the treatment of auricular fibrillation reported from the Massachusetts General Hospital, the authors advocated digitalization in those cases complicated by congestive failure. The successful action of quinidine in terminating arrhythmias in digitalized animals has been convincingly demonstrated in experiments recently reported by Haskell.<sup>13</sup>

In the present series of cases, most of the patients received digitalis prior to treatment with quinidine. The data already presented point to the favorable influence of previous digitalization on the restoration of normal rhythm by means of quinidine sulphate. At any rate, our observations do not bear out the contention of some authors that digitalis antagonizes the successful action of quinidine. In addition, many of the digitalized patients received the smallest doses of quinidine used in the entire series, with restoration of normal rhythm, corresponding to the earlier experience in this hospital. This view, again, is in disagreement with those observers who believe that previous digitalization

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8 Cantani, quoted by Haskell, C. C. The Influence of Quinidin on the Cardiac Irregularity Produced by Digitalis, *J. Pharmacol. & Exper. Therap.* **32**: 223, 1928.

9 Schott, E. Zur Frage der Chinidintherapie, *Deutsches Arch. f. klin. Med.* **134**: 208, 1920.

10 Korns, H. M. An Experimental and Clinical Study of Quinidin Sulphate I. Experimental, *Arch. Int. Med.* **31**: 15 (Jan.) 1923.

11 Frey, W. Weitere Erfahrungen mit Chinidin bei absoluter Herzunregelmässigkeit, *Berl. klin. Wchnschr.* **55**: 849, 1918.

12 Frey, W. Chinidin zur Bekämpfung der Absoluten Herzunregelmässigkeit (Vorhofflimmern), *Deutsches Arch. f. klin. Med.* **136**: 70, 1921.

13 Haskell, C. C. The Influence of Quinidin on the Cardiac Irregularity Produced by Digitalis, *J. Pharmacol. & Exper. Therap.* **32**: 223, 1928.

necessitates the subsequent use of larger doses of quinidine. Furthermore, we have failed to observe any undesirable effects which could be attributed to the combined use of both drugs.

Our opinion, therefore, based on our observations and on experimental and theoretical considerations, is that previous digitalization is justified as a preliminary step in the treatment of all patients with auricular fibrillation by means of quinidine sulphate. Our experience has led us to believe that such preliminary treatment is an important factor in the successful use of quinidine in some cases, and that occasionally it may be the deciding factor between failure and success. That the treatment may be consummated with smaller doses of quinidine is a further advantage of considerable importance, since we have seen patients who were so sensitive to quinidine that 3 grains (0.19 Gm.) have caused toxic symptoms coincidentally with the restoration of normal rhythm. It would appear, from a study of our cases, that the best results are obtained when digitalis is administered in doses sufficient, at least, to bring about inversion of the T wave in leads 1 and 2 of the electrocardiogram.

In emphasizing the value of digitalis, and in stating that it should be used as a matter of routine in every patient, it is not our intention to convey the impression that it is indispensable in all cases, since this would be contrary to fact. Indeed, it may be properly argued, on theoretical grounds, that digitalization, prior to the administration of quinidine, may interfere with the successful action of the latter drug in a rare case. It is presumably on the basis of such considerations that some physicians oppose the use of digitalis in these cases. Actually, we have never seen a case in which failure to restore normal rhythm could be definitely attributed to the use of digitalis, although such a possibility must be conceded.

#### REPORT OF CASES

In studying the problem of digitalization in this connection, we have been much more impressed by the observation of individual cases than by the statistics of the entire series. The following case in our series is a good illustration of the value of preliminary digitalization.

CASE 1.—A patient who had had fibrillation for many years was given a course of quinidine treatment, comprising over 150 grains (9.72 Gm.) of quinidine sulphate in five days. Normal rhythm was not restored. Five years later his condition was entirely unchanged so far as could be determined by careful questioning, physical examination and electrocardiographic study. The fibrillation by this time had a duration of at least fifteen years. Before quinidine was given, the patient was completely digitalized, so that the T waves in leads 1 and 2 were inverted. In three days, a total dose of 108 grains (6.99 Gm.) of quinidine sulphate restored normal rhythm without any untoward incident.

The relation of digitalization to the dosage of quinidine is shown in case 2

CASE 2—F J M, a man, aged 43, had had auricular fibrillation constantly for nine weeks. Following complete digitalization he was given two test doses of quinidine sulphate, 3 grains (0.19 Gm) each, in three hours. This was sufficient to restore normal rhythm. Two and one-half years later he awoke in the morning in a paroxysm of fibrillation, the first since normal rhythm had been restored. Without previous digitalization he was started on quinidine, 30 grains (1.94 Gm), or five times the amount used two and one-half years earlier, had to be given before normal rhythm was restored. His condition was similar in every way to that during the earlier attack, except that the fibrillation was then of nine weeks' duration, and now had existed only a few hours when quinidine therapy was started.

In cases of auricular flutter the same beneficial action of digitalis may be observed, as illustrated by case 3.

CASE 3—A patient had an auricular flutter of fifteen months' duration. He was given a total dose of 159 grains (10.30 Gm) of quinidine in eight days, without the restoration of normal rhythm. He was then digitalized, and normal rhythm was restored by 72 grains (4.66 Gm) of quinidine sulphate in two days. Digitalization did not produce fibrillation in this case, so that we consider the final result as due chiefly to quinidine and not to digitalis.

The factors controlling circus movement in the auricle are (1) the length of the path traversed by the wave, (2) the duration of the refractory period at any one point, and (3) the speed at which the wave is conducted<sup>11</sup>. By closing the gap between the crest and the wake of the circulating wave, circus movement may be interrupted and normal rhythm restored. This may be accomplished by (1) increasing the refractory period sufficiently, the other factors remaining constant, or by (2) increasing the rate of circus movement, the other factors remaining constant. Practically, these effects are interrelated, and the actual situation is a complicated one, the final result in any given instance depending on the preponderance of one effect over the other.

One of the constant effects of quinidine is to decrease the rate of circus movement<sup>14</sup>. The most striking result of quinidine, according to Lewis and his co-workers, is the increase of the refractory period, often amounting to 50 per cent or more. Under these conditions

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<sup>14</sup> Cohn, A. E., and Levy, R. L. Experiments with Quinidin on Conduction and on the Refractory Period in the Dog's Heart, *Proc. Soc. Exper. Biol. & Med.* **19** 174, 1921-1922. Drury, A. N., and Iliescu, C. C. The Restoration of the Normal Cardiac Mechanism in Cases of Auricular Fibrillation by Means of Quinidin Sulphate, *Brit. M. J.* **2** 511, 1921. Lewis, T., Drury, A. N., Iliescu, C. C., and Wedd, A. M. The Manner in Which Quinidin Sulphate Acts in Auricular Fibrillation, *Brit. M. J.* **2** 514, 1921.

normal rhythm is restored only in those cases in which the effect on the refractory period predominates over the effect on the rate of circus movement

Digitalis, like quinidine, acts directly on the muscle of the heart, and indirectly by stimulation of the vagus nerve, the effects being in opposite directions. Because one effect predominates in some instances and the other in the remaining instances, it is impossible to predict the action of digitalis in a given case. The usual effect, however, according to Lewis,<sup>15</sup> is an increase in the rate of circus movement. The conversion of flutter to fibrillation by digitalis is probably explained in this way.

The administration of quinidine following digitalization reduces the rate of circus movement to the same extent that it does in the absence of digitalis. The final circus rate, however, is definitely higher when digitalis has been used, since the rate is thereby higher when quinidine is started. Assuming now that quinidine has lengthened the refractory period of auricular muscle as much as when digitalis has not been used, the possibility of closing the gap is improved under the combined effects of quinidine and digitalis. The smaller the gap between the crest and wake of the circulating wave, the easier it is to close. Furthermore, the combined use of the drugs may favor the predominance of effect on the refractory period over that on the rate of circus movement, this would be significant in view of the nice balance which ordinarily exists. Finally, it is possible that digitalis causes the wave to circulate in a shorter path, which accounts in part for the increased rate of circus movement. That this takes place when flutter is converted to fibrillation under the influence of digitalis can hardly be doubted, such a change, moreover, facilitates the ease with which the gap may be closed.

We may say then, that although digitalis produces an effect on the fibrillating auricle opposite to that produced by quinidine, theoretically the combined action of the two drugs may favor the termination of circus movement. We may expect, under such conditions, to succeed with smaller doses of quinidine, and this actually has been our experience.

Digitalization is of value in preventing ventricular tachycardia, which is a frequent annoying result of the reduction in the rate of circus movement. In patients with slight congestive failure or limitation of reserve, it is to be expected that digitalization will improve their general condition.

A possible, but unproved, effect of digitalization is the prevention of fixed flutter which may result from quinidine therapy and which may be distressing and even fatal.

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15 Lewis, T. *The Mechanism and Graphic Registration of the Heart Beat*, New York, Paul B. Hoeber, 1925.

## UNTOWARD RESULTS FROM QUINIDINE THERAPY

A number of patients complained of the minor manifestations of cinchonism—tinging in the ears, slight deafness, fulness in the head, headache, flushing, dizziness, itching of the skin and diarrhea. One patient died suddenly, but in reviewing the circumstances, it seemed unlikely that her death was due to quinidine. The patient was a woman, aged 46, with hypertension, hypertensive heart disease and auricular fibrillation which had been paroxysmal for four years and constant for two months before quinidine was given. Normal rhythm was restored by 96 grains (6.22 Gm.) of quinidine taken during a period of five days, without any toxic effects from the drug. After twenty-four hours, auricular fibrillation recurred. When last seen, the patient apparently was in good condition, the pulse rate being 80 per minute and irregular. Twenty-five minutes later, while sitting on the bed pan, she died suddenly. Autopsy was not permitted.

As is usual, transitional auricular flutter was observed in several patients, in the course of a change from auricular fibrillation to normal rhythm, but in this series fixed flutter did not occur.

In one patient a regular ventricular rhythm at the rate of 70 per minute without evident P waves in any of the customary axial leads occurred after several doses of quinidine. In later electrocardiograms one P wave was evident. Quinidine had to be discontinued on account of symptoms of cinchonism, and auricular fibrillation shortly recurred. Two other cases with regular ventricular tachycardia without evident P waves occurring as a result of quinidine therapy have come under our observation. These three cases will form the subject of a separate communication. From observation of these cases we believe it likely that standstill of the whole heart may explain some of the reported fatalities during quinidine therapy which were hitherto unexplained.

## COMMENT

In the series reported previously from the Massachusetts General and New Haven Hospitals,<sup>3</sup> the first sixty of the total of seventy-five patients were practically unselected. The cases studied for the present report were all selected, one of the considerations being the probability of success according to the generally accepted criteria. Yet in the first series, in 68 per cent of the cases the rhythm was restored to normal and in the second series, in only 65.7 per cent. Our attention is arrested by this comparison, and it is pertinent to inquire into the meaning of the failure of selection to raise the number of favorable responses.

Following the work of Lewis we may attribute the termination of "fibrillation by quinidine to a predominant influence upon the refractory period," and the failure of quinidine "to its balancing or predominating influence on conduction," the balance ordinarily being a nice one. In

practice this may mean that in any series of cases in which the patients are properly treated the number responding to quinidine therapy will vary within small limits. Korns,<sup>16</sup> from a clinical study of his cases, finds "support for the theory that the action of quinidine in abolishing circus movement is not conditioned by the type of cardiac lesion, degree of decompensation, duration of fibrillation, etc., but is essentially related to the pathologic physiology of the auricular muscle."

We can hardly overlook the fact, however, that various factors may have considerable influence, and perhaps all the more so because quinidine effects a nice balance, at least in experiment, as it changes the refractory period and conduction in auricular muscle. Moreover, there is a greater difference in the degree of success attained with quinidine in the numerous series of cases reported in the literature than can be explained entirely on the basis of proper or improper treatment. And finally, a study of our cases indicates to us that certain factors, already discussed, do have a bearing on the outcome of treatment.

In judging the value of quinidine in general or in any one particular case, the permanence of the result obtained by its successful use is the most important consideration. If the restored normal rhythm is to be but a transitional state between two periods of permanent auricular fibrillation, it is best not to resort to the use of quinidine in this condition. The patient cannot be benefited by such treatment, and he has been exposed to the toxic action of the drug and to the danger of embolism. It is from this point of view especially that the selection practiced in this series of cases has appeared to be successful, as may be seen by referring to the follow-up study presented, for in the second series the number of "permanent" restorations of normal rhythm is much greater than in the first series.

That quinidine is a valuable drug, and that it is desirable to continue its use in permanent auricular fibrillation, is clearly evident from the large number of cases that we have now been able to follow for a number of years after the restoration of normal rhythm. There can be no doubt that these patients have been benefited by the drug.

#### QUINIDINE THERAPY IN OTHER CONDITIONS

We have had an opportunity to observe the effect of quinidine in twenty-nine cases of paroxysmal auricular fibrillation and two of paroxysmal auricular flutter. Most of these patients have been observed for a long period of time, from seven to eight years in the oldest cases. In sixteen of the patients with fibrillation, quinidine was beneficial, in

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<sup>16</sup> Korns, H. M. An Experimental and Clinical Study of Quinidin Sulphate. II. Clinical, Arch Int Med **31**: 36 (Jan) 1923.

five patients quinidine was of no value, in three patients its action was doubtful in one patient it appeared to be effective at first but later not only was it ineffective but it appeared to aggravate a regular tachycardia which occurred in addition to the paroxysms of fibrillation, and in four patients the action of quinidine could not be determined, in two of these on account of sensitiveness to the drug. A patient in whom quinidine was ineffective for the paroxysms of fibrillation found the drug useful for paroxysms of ventricular tachycardia. One of the patients in whom the action of quinidine on the fibrillation was doubtful had frequent premature beats which were effectively controlled by the quinidine. digitalis proved effective in stopping the paroxysms of fibrillation in this patient. The beneficial effect of digitalis was seen in one other patient in whom quinidine appeared to be entirely ineffective.

The beneficial action of quinidine was manifested in five patients by the termination of the paroxysms of fibrillation in three patients quinidine was useful in reducing the number of paroxysms, while in four patients the number of paroxysms was reduced and the attacks were shortened. In three patients the paroxysms of fibrillation did not recur after rations of quinidine had been taken for a short period of time.

While quinidine appeared to be of definite value in 64 per cent of the patients with paroxysmal auricular fibrillation in whom the action of the drug could be estimated, other measures of treatment were resorted to in these patients, and these undoubtedly had some influence on the outcome of treatment. Reassurance, regulation of diet, avoidance of fatigue, improvement of the general physical condition and other such measures have contributed to the success of treatment.

One patient with paroxysmal flutter found quinidine ineffective, although digitalis seemed to be of value. The second patient with paroxysmal flutter took 18 grains (1.16 Gm.) of quinidine daily with almost constant regularity for about seven years. Although he had a daily paroxysm of flutter he felt worse when not taking quinidine. He had no toxic symptoms from the constant use of quinidine. Digitalis appeared to make him worse.

Quinidine was effective in a small group of patients with either paroxysmal tachycardia or premature beats. In one patient with paroxysmal tachycardia quinidine was beneficial at first but later became ineffective, then digitalis was found to be effective. In another patient, quinidine successfully stopped some attacks of tachycardia, in others it did not, although digitalis was effective. A third patient had paroxysmal auricular fibrillation and paroxysmal ventricular tachycardia. Quinidine was effective for the paroxysmal ventricular tachycardia, although it had no influence on the fibrillation.



## SUMMARY AND CONCLUSIONS

This paper consists primarily in a clinical study of the action of quinidine sulphate in sixty-two cases of permanent auricular fibrillation, eight cases of permanent auricular flutter, twenty-nine cases of paroxysmal auricular fibrillation, two cases of paroxysmal auricular flutter, and a small group of cases with paroxysmal tachycardia and premature beats. A follow-up study of a series of seventy-five additional cases of permanent auricular fibrillation and flutter reported in 1923 is also presented. We have reached the following conclusions from a study of this material:

1 In the series of seventy cases, comprising sixty-two of permanent auricular fibrillation and eight of flutter, normal rhythm was restored in 65.7 per cent.

2 In apparently normal hearts (seven cases), permanent auricular fibrillation was terminated by quinidine in 100 per cent of the cases, irrespective of the age of the patient and the duration of the fibrillation. These patients are the most satisfactory to treat.

3 The next most responsive group is that of patients with rheumatic heart disease who are less than 41 years of age.

4 In the hyperthyroid group the response is somewhat better than in the group of patients with hypertensive and arteriosclerotic heart disease.

5 When not dealing with normal hearts the most important single factor which influences the outcome of the treatment is the duration of fibrillation. This is true in a limited sense only, for the response is surprisingly high when the fibrillation has lasted less than a month, beyond this, duration apparently is of little or no importance.

6 Age is important in the group of patients with rheumatic heart disease. The desired response occurs in a high percentage of the young patients, but occurs in a much smaller proportion of the patients more than 40 years of age.

7 Etiology has but a minor influence on the response to quinidine therapy.

8 Recent congestive failure reduces the probability of success from the use of quinidine, the duration of fibrillation has not accounted for the poor response in the cases with congestive failure.

9 Factors contributing to failure in some of our cases were insufficient quinidine dosage, intercurrent infections and possibly alcoholism.

10 A past history of congestive failure, the size of the heart when enlarged, the type of fibrillation and sex appear to be of no influence on the outcome of treatment. In each of the ten patients with normally sized hearts normal rhythm was restored.

11 The history of fibrillation for a great many years, in the absence of valvular disease and congestive failure, recent or present, is not a contraindication for quinidine therapy

12 It seems highly desirable to digitalize all patients as a matter of routine before starting quinidine. Full therapeutic doses should be used. There is clinical, experimental and theoretical justification for this view. Digitalization is not indispensable in many cases, but in some it will spell the difference between failure and success. Often normal rhythm may be attained with smaller doses of quinidine if digitalization has been resorted to. It may add to the comfort of the patient, improve his condition and possibly prevent fixed flutter. No harm has been observed from the combined use of digitalis and quinidine.

13 In this new group of seventy patients there was one death which might possibly be attributed to quinidine, but probably was not due to it.

14 The most frequent change of mechanism noted in the electrocardiogram was flutter, but in no case was it fixed. In the entire series of patients receiving quinidine in the Massachusetts General Hospital there were two cases exhibiting probable auricular standstill. A third case was seen in a private patient. It seems likely that some of the fatalities reported during quinidine therapy may have resulted from the standstill of the whole heart.

15 Quinidine is of value in preventing and terminating paroxysmal auricular fibrillation, and is effective in some cases of paroxysmal tachycardia and premature beats.

16 In cases of auricular flutter, digitalis is probably more effective than quinidine. Digitalis appears to be more effective than quinidine in occasional cases of paroxysmal auricular fibrillation and paroxysmal tachycardia.

17 In judging the value of quinidine in permanent auricular fibrillation, the criterion of greatest importance is the permanence of the results obtained. Our follow-up studies have indicated that (1) restored normal rhythm is "permanent" in a significant number of patients, and (2) although there is no definite evidence that normal rhythm prolongs life or reduces mortality, it is clearly evident that it promotes the health of the patient.

# THE EFFECT OF DIGITALIS ON THE ELECTROCARDIOGRAM

AN EXPERIMENTAL STUDY ON DOGS AND CATS \*

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Considerable attention has been paid to the electrocardiographic changes, particularly of the T wave, following the administration of digitalis. Experiments performed on human beings and on animals have not given the same results in the hands of different observers. Pardee,<sup>1</sup> using normal persons and patients with heart disease, found that the T wave began to decrease in amplitude as early as from two to four hours after the administration of tincture of digitalis in doses of 1 minim (0.06 cc) per pound of body weight. The maximum effect was seen in from six to seven hours, and the change lasted for about twenty-four hours. The same author stated later that similar effects were noted with much smaller doses, in fact, with from one sixth to one eighth of the dose previously mentioned. Pardee<sup>2</sup> considered a change in the T wave as a reliable sign not only of the beginning action but also of the absorption of digitalis, and suggests this as a criterion for the effect of digitalis and as a method of standardization. He<sup>3</sup> used this method in comparing the effect of digitalis when given by the oral, hypodermic and intravenous routes.

In 1915, Cohn, Fraser and Jamieson<sup>4</sup> described the depression of the T wave following the administration of digitalis. They observed that the change in the T wave preceded the appearance of nausea or changes in the rhythm or conduction time. In human beings, the depression of the T wave developed into a negative wave after a dosage of 1.2 Gm of dried digitalis leaves. Similar results were obtained by Marvin, Pastor and Carmichael<sup>5</sup> in patients before an operation.

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\* From the Institute of General Experimental Pathology of the University of Vienna, Prof C J Rothberger, Director

1 Pardee, H E B. Rate of Absorption of Digitalis from the Gastro-Intestinal Tract. Clinical Study, J A M A **75** 1258 (Nov 6) 1920

2 Pardee, H E B. Standardization of Digitalis by Its Action on Human Heart, J A M A **81** 186 (July 21) 1923

3 Pardee, H E B. Hypodermic Digitalis Preparations, J A M A **85** 1359 (Oct 31) 1925

4 Cohn, A E, Fraser, F R, and Jamieson, R A. J Exper Med **21** 593, 1915

5 Marvin, H M, Pastor R B, and Carmichael, M. Electrocardiogram and Blood Pressure During Surgical Operation and Convalescence, Arch Int Med **35** 782 (June) 1925

was performed Harris<sup>6</sup> also reported such changes Cohn and Stewart<sup>7</sup> reported that they found a change in the T wave constantly in dogs after intravenous injections of tincture of digitalis or digifoline They gave digitan by mouth and also found a changed T wave Robinson and Wilson<sup>8</sup> injected tincture of digitalis into cats They injected one tenth of a previously determined minimal lethal dose intravenously every ten minutes, and made electrocardiographic tracings at intervals of one, five and nine minutes after each injection The vagi were intact in one series of experiments and cut in another Their results showed that a negative T wave occurred when about one fourth of the minimal lethal dose was injected and that prolonged conduction time and complete dissociation occurred only after the administration of larger doses These authors stated the belief that a change in the T wave is the first evidence of digitalis intoxication and that the vagi have no marked effect on the production of this change

Other observers reported that the T wave becomes larger after injection of digitalis Yacoel and Papanayotou<sup>9</sup> gave digitalis to patients with heart disease, and concluded that an increased amplitude of the T wave along with other changes are signs of improvement Selenin,<sup>10</sup> using dogs under morphine narcosis, found that therapeutic doses of digitalis given intravenously caused an enlarged T wave Bickel and Tsividis<sup>11</sup> used rabbits and gave Focke's extract of digitalis intravenously They found that doses up to 1 cc per kilogram of body weight caused an increase in the T wave, while larger quantities caused a smaller wave In another series of experiments, Bickel and Pavlov<sup>12</sup> found that ordinary doses of digitalis and strophanthus caused an increase in the size of the T wave and that this wave later became negative Similar results were obtained by Straub<sup>13</sup> Nicolai and Simons<sup>14</sup> gave powdered digitalis in doses of 0.1 Gm three times a day for five days The amplitude of the wave was found increased in these persons

#### METHOD

These conflicting reports suggested a series of experiments to determine the effect of varying doses of digitalis Dogs were used at first, later cats The

6 Harris, J Lancet, March 30, 1918

7 Cohn, A. E., and Stewart, H. J. J. Clin. Investigation **6** 53 (Aug. 20) 1928

8 Robinson, G. C., and Wilson, F. N. J. Pharmacol. & Exper. Therap. **10** 491 (Jan.) 1918

9 Yacoel, J., and Papanayotou, D. Arch. d. mal. du coeur **20** 24, 1927

10 Selenin, W. P. Arch. f. d. ges. Physiol. **143** 137, 1912

11 Bickel, A., and Tsividis, A. Biochem. Ztschr. **45** 462, 1912

12 Bickel, A., and Pavlov, M. Biochem. Ztschr. **48** 459, 1913

13 Straub, H. Ztschr. f. Biol. **53** 523, 1910

14 Nicolai, G. F., and Simons, A. Med. Klin. **5** 160 (Jan. 31) 1909

animals were weighed daily and were carefully watched for vomiting and other signs of intoxication. Subcutaneous injections of ethyl carbonate (urethane) were given in sufficient doses to keep the animal quiet but not enough to cause sleep. A control dog, which had a negative T wave normally and without the use of digitalis, was given the usual quantity of urethane, and an electrocardiogram was made one hour later to determine the effect on the T wave. No change was observed. All electrocardiograms were made with needle leads, one lead being from arm to arm, the other from the base of the neck to the left groin. Chest leads were used in cats instead of the arm to arm leads, the needles being inserted at each side of the thorax, while the longitudinal leads remained the same as for dogs.

The powdered digitalis leaves were standardized. The other forms of digitalis consisted of digalen, Hoffmann La Roche, digitalin, Nativelle, digipuratum, Knoll (now described in "New and Nonofficial Remedies" as digitan), and digitalis dispers, Krause. The smaller doses corresponded to therapeutic quantities in man when calculated according to the respective weights of man and of the animals used, however, much larger, even fatal, doses were also used. The drug was also given daily to observe the cumulative effect.

Control electrocardiograms were taken before each experiment. Further tracings were taken at intervals of three, six and twenty-four hours after the administration of digitalis. The tracings in acute experiments were taken at intervals of ten or fifteen minutes for periods of about three hours and again fifteen and twenty-one hours later if the animal survived.

#### EXPERIMENTS

The first series of experiments consisted in noting the changes following the administration of powdered digitalis leaves by mouth with the aid of a stomach tube.

A dog weighing 4,500 Gm was given 0.004 of standardized digitalis leaves by mouth once daily for four days. There was practically no change in the electrocardiogram except a slowing of the heart rate from 275 to 195 per minute. The T wave remained the same as in the control.

Another dog, weighing 7,000 Gm, received 0.008 of powdered digitalis leaves in the same way for four days. Larger doses were then tried. A dog weighing 5,100 Gm was given 0.016 of digitalis for four days. A male dog, weighing 5,900 Gm, received 0.024 daily for three days, then 0.048 twice daily for two days and then 0.104 once on the next day, making a total of 0.368 in six days. Another dog, weighing 4,400 Gm was given 0.032 once daily for three days, then 0.128 daily for two days, making a total of 0.352 in five days. In the electrocardiograms made of the foregoing animals, the T wave occasionally increased in amplitude by 1 or 2 mm, but this was rare. In none of these tracings was there a reduction in the amplitude of the T wave, and the wave never became negative. The only change constantly present was a definite reduction in rate, which might have been due to the fact that the animals became accustomed to the procedures.

The failure to record changes in the T wave, even after large doses of digitalis by mouth might be due, perhaps, to the nonabsorption from the gastro-intestinal tract. To exclude such a possibility subcutaneous administration was tried. A dog weighing 5,700 Gm was given 3 cc of digalen, Hoffmann La Roche, subcutaneously, and electrocardiograms were taken three, six and twenty-four hours later. A change was not observed, and vomiting did not occur. The animal was given 5 cc on the next day and 5 cc again on the day following, making a total of 13 cc in three days. There was a slight reduction in the amplitude of the R and S, and the T wave became somewhat lower for a while, but its height at the end of the experiment was exactly the same as in the control. A negative T wave was never observed. The same animal was then given 10 cc subcutaneously and died three hours later.

Intramuscular injections of digitalin, Nativelle, were then employed. A female dog, weighing 8,700 Gm, was given 0.5 mg of digitalin in olive oil intramuscularly. Another 0.5 mg was given on the next day and 1 mg on the following day, making a total of 2 mg in three days. The electrocardiograms, taken at intervals of three, six and twenty-four hours after each injection, did not show a deviation from those of the control tracings, and the T wave became neither lower nor negative.

The intravenous route was next chosen. A dog weighing 4,400 Gm was given digitalis dispart, Krause, the standardized strength being 150 frog doses in 0.1 Gm. The total dose of 200 mg was divided into small doses and given during a period of three hours. Electrocardiograms were taken every fifteen minutes. The heart rate dropped from 225 to 156 per minute, and the PR interval increased from 0.08 to 0.12 seconds. This change occurred at the end of the first hour, after 75 mg had been injected intravenously. No additional changes occurred during the rest of the experiment or in a tracing taken fifteen hours later. The T wave did not show a change at any time, even when the heart rate dropped and the PR interval was prolonged.

Digipuratum, Knoll, was then injected intravenously. This preparation was found satisfactory and was used in all further experiments. The dog which failed to react to intramuscular injections of digitalin was used on the following day, after another control electrocardiogram had been made. The animal received 2 cc intravenously. Tracings were made at intervals of ten and fifteen minutes for a period of two hours. Subsequent tracings were made three, twenty-one and twenty-seven hours later. There was practically no change in the electrocardiogram at any time. The same dog was used for a more acute experiment after the last tracing was taken. Electrocardiograms were taken every ten and fifteen minutes during the experiment, which lasted two hours. The first dose of digipuratum given intravenously was 4 cc. Distinct

changes were seen in the electrocardiogram in thirty minutes. The heart rate dropped from 168 to 96, the PR distance was increased from 0.08 to 0.12 seconds, and the amplitude of the T wave was reduced from 4 to 2 mm. The value of this reduction is doubtful, as a control tracing from the same dog, taken four days earlier, showed a T wave of only 3 mm. A change of 1 or 2 mm seems indecisive. Another injection of 2 cc did not produce further changes in the wave, but the amplitude of R and S was reduced. Another dose of 4 cc was given, and ventricular tachycardia occurred. The animal died shortly afterward. This experiment showed that a negative T wave did not appear, and that this wave became reduced only by 1 or 2 mm even though the drug was given until death was caused. The slight variability in the electrocardiogram taken for control on different days discounts an equally slight change in the T wave after the administration of digitalis.

Another dog was given smaller doses of digipuratum intravenously, and electrocardiograms were taken every fifteen minutes for two and a half hours and again in sixteen hours. The animal weighed 6,200 Gm and received 2 cc as the first dose after a control tracing had been made. Vomiting occurred in five minutes, but there was no change in the electrocardiogram at this time. Another injection of 2 cc was given thirty minutes later, and an electrocardiogram taken thirteen minutes after this dose showed definite changes. The heart rate dropped from 195 to 120, the PR interval increased from 0.06 to 0.16 seconds and there was marked sinus arrhythmia at times, heart block and escaped beats were present and ventricular extrasystoles were seen. All of these changes appeared at the same time, none was present before. The T wave was unchanged. A further dose of 1 cc was given thirty minutes after the last one, and the T wave remained unchanged. The other signs of toxicity persisted. Another dose of 1 cc was then given, making a total of 6 cc for a dog weighing 6,200 Gm in a period of two and a half hours. Ventricular tachycardia now developed. A tracing taken fifteen hours later showed a return to sinus rhythm, but the PR interval was still 0.04 seconds longer than on the control tracing. The T wave was unchanged, slightly higher if anything. The digipuratum in this experiment was given until definite toxicity occurred, but the T wave never became negative. In fact it was slightly higher at the end than at the beginning of the experiment. An interesting feature was the fact that none of the dogs that received digitalis developed coupled beats. Even toxic or fatal doses failed to produce this phenomenon in contrast to the frequent occurrence in cats.

A similar but smaller series of experiments was made on cats. Digipuratum was given intravenously at intervals of thirty minutes, and electrocardiograms were taken every ten or fifteen minutes for the

two and a half or three hours that the experiments lasted. The cats were weighed and received sufficient doses of ethyl carbonate (urethane) subcutaneously to keep them quiet but not enough to put them to sleep. Needle leads were used as previously described. Control tracings were taken before the drug was given.

A cat, which weighed 2,100 Gm, was given 2 cc of digipuratum intravenously and tracings were made at fifteen minute intervals for a period of three hours. Salivation and vomiting occurred in seven minutes, and the electrocardiogram taken fifteen minutes after the injection showed idioventricular rhythm. Another tracing taken fifteen minutes later still showed idioventricular rhythm, but the ventricular beats were of two varieties, one form alternating with the other, forming coupling. Later records showed complete block, but the T wave remained positive except in two tracings in which the T wave was diphasic. A distinctly negative T wave was not seen although there were signs of severe intoxication before the wave reappeared in conducted beats. The animal subsequently developed ventricular tachycardia.

Another cat weighing 3,800 Gm was given digipuratum intravenously in smaller doses, which were repeated. The experiment was performed as with the first animal. The first dose was 0.5 cc and the heart rate was reduced from 210 to 165 per minute. The T wave was positive in the chest leads of the control and negative in the longitudinal lead of this curve. The wave became iso-electric in the first lead thirty minutes after the injection and remained slightly negative for the remainder of the experiment. The longitudinal lead remained practically unchanged. Other signs of intoxication developed, such as vomiting and finally idioventricular rhythm, which in places consisted of coupled ventricular beats of different types. This animal received a total of 1.5 cc of digipuratum intravenously.

A cat weighing 2,200 Gm received 0.5 cc of digipuratum intravenously and then 0.25 cc every thirty minutes until a total dose of 1.25 cc was given. The heart rate fell from 216 to 168. The R was reduced from 6 mm to nearly zero, and the T wave became negative fifteen minutes after the first dose. Complete block and idioventricular rhythm appeared later, in seventy-five minutes. This animal also showed coupling of two different varieties of ventricular beats.

A cat, which weighed 2,900 Gm, was given digipuratum intravenously under the same conditions as the previous animals until a total of 1.75 cc was administered. The heart rate was decreased only slightly, the R gradually became smaller, from 14 mm in the control to 5 mm. The T wave at first became slightly negative and then returned as a positive wave about thirty minutes before idioventricular rhythm set in.



## COMMENT

Experiments on dogs in which various preparations and doses of digitalis were given by different routes showed results which were different from those reported by other investigators. The report of Cohn and Stewart,<sup>7</sup> which stated that dogs which received sufficient amounts of digitalis constantly showed changes in the T wave, could not be corroborated. There is no question of sufficiency of dosage in my experiments, as the dogs showed other evidences of intoxication, such as heart block, auriculoventricular and ventricular rhythms and vomiting. In some instances, the drug was given until death resulted.

These experiments on dogs also showed that several of the electrocardiographic evidences of intoxication all appeared at about the same time. This is in contrast to the results of Robinson and Wilson,<sup>8</sup> who experimented on cats and found that a change in the T wave preceded block and dissociated rhythm. The fact that different animals were used must be kept in mind.

Another interesting feature was that coupling was not observed in dogs regardless of the quantity of digitalis given. This is in contrast to the results obtained with cats.

The rapidity of intravenous action was demonstrated in dogs when sufficient quantities were given. A dog that received 4 cc of digituratum intravenously vomited in thirteen minutes, and heart block was present thirty minutes after the injection.

A constantly negative T wave was not observed in a single instance in dogs in spite of the fact that sufficient quantities were given to produce distinct signs of marked toxicity. It may be stated in passing that some animals are more susceptible to digitalis than others of the same species. Magnus<sup>15</sup> told of two varieties of cats from the same city, one being more resistant to digitalis than the other. This can hardly be the case in my experiments, as there were many other evidences of toxicity showing that the drug was sufficiently effective.

These results throw some doubt on the advisability of using the T wave as a criterion of the activity of digitalis in man. It is, of course an open question whether the results of experiments on dogs can be transferred to man, but the failure to observe a negative T wave in a single instance and the reports previously mentioned on man, which contradict the statement that a change in the T wave is a sign of digitalis action, seem to show the advisability of at least further study on this question before definite conclusions can be reached.

The experiments on cats were less clearcut and of less value because a smaller number of animals were used. Unforeseen circumstances made it imperative to cut short the experiments. It may be stated,

however, that a negative T wave was not a constant observation even though the amount of digitalis was pushed to extreme toxicity. A serious objection also is the fact that the T wave was negative at one time and later positive during the same experiment after more of the drug was given. Further study is necessary before definite conclusions can be drawn in this respect.

#### SUMMARY

1 Dogs were given various preparations of digitalis in different doses and by various routes. The quantities given varied from what would correspond to therapeutic doses to quantities causing definite toxicity and death.

2 Electrocardiograms taken at frequent intervals and over a long period of time failed to show a constantly lowered T wave. The wave was never seen to be negative.

3 Intravenous administration produced effects in a few minutes when the dose was sufficiently large.

4 It seems an open question whether the T wave can be used as a criterion of the action of digitalis.

5 Experiments on a small series of cats produced variable results. The T wave sometimes became negative and at other times remained unchanged. The observation that the wave may become negative for a time and then return as a positive wave after more digitalis was given seems to point to the necessity for more study with these animals.

# OPIUM ADDICTION

## IV THE BLOOD OF THE HUMAN ADDICT DURING THE ADMINISTRATION OF MORPHINE<sup>\*</sup>

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In this paper, we present the data obtained from the study of blood drawn from a series of human addicts receiving morphine sulphate hypodermically in sufficient quantity to prevent withdrawal symptoms. All of these addicts exhibited the so-called withdrawal symptoms on cessation of administration of the drug. These symptoms have been described in a previous paper by us<sup>1</sup> and are well known to any one familiar with the drug problem. Our purpose in this study has been twofold. The first objective was to search for possible changes in the physicochemical properties of the blood of these addicts, our second, to obtain values in addicts receiving the drug for comparison with the results obtained from the same addicts following the withdrawal of the drug.

### EXPERIMENTAL PROCEDURE

During this study the addict received the quantity of drug required, which was administered to him by the nurse in charge of the ward. As a rule, the same quantity sufficed from day to day for each subject, but any minor disturbance in the ward on the part of other refractory patients always resulted in a need for a greater amount. This variation of dosage is common among addicts at liberty with a supply of the drug at hand. The slightest degree of fear on their part always resulted in a temporary increase in dosage. The dosage of the drug in the cases studied varied from 6 to 30 grains (0.4 to 1.95 Gm.) of

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<sup>\*</sup> From the Narcotic Wards of the Philadelphia General Hospital

<sup>\*</sup> Expenses of this research were defrayed by the Committee on Drug Addictions, New York City. The research was carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction in the wards of the Philadelphia General Hospital, which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia.

1 Light Arthur B, and Torrance, Edward C. Opium Addiction. I. The Conduct of the Addict in Relation to Investigative Study, Arch Int Med 43 206 (Feb) 1929

# THE RÔLE OF ALLERGY IN TUBERCULOSIS <sup>†</sup>

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## DEFINITION OF ALLERGY

When the animal body becomes infected with tubercle bacillus, its reactive powers soon become profoundly altered. This deep-seated alteration is in many respects imperfectly understood, but it manifests itself in at least two important ways. In the first place, tubercle bacilli cannot thrive as well in the previously infected body as in the normal one, i. e., an immunity is developed which, while admittedly incomplete, is nevertheless of the greatest importance in restraining the growth of, and preventing further invasions by, the bacillus. In the second place, this immune body is abnormally susceptible to protein derived from the body of the tubercle bacillus. Locally, amounts of tuberculo-protein that are rather harmless to the normal body produce necrosis of tissue and intense inflammation in the infected one. Intravenously, amounts that will be ignored by the normal body promptly produce fever, prostration and even death in the infected one. In other words, after infection the body becomes hypersensitive, or "allergic," to the protein of the bacillus. In the pathogenesis of tuberculosis, this allergic condition plays a rôle which is no less important than that of immunity. It is a direct agent of tissue destruction, its presence or absence determines to a considerable degree the character and the extent of the lesions and symptoms which will result from infection with the tubercle bacillus, and there are many who believe that it is only through allergy that immunity can operate.

It is important to define clearly at the outset just what phenomena are to be included in the term "allergy," for different writers mean somewhat different things when they speak of the "allergic reaction." All recognize that the allergic body reacts more violently to the bacillus than does the normal one, but whether the difference in reaction is qualitative or merely quantitative, whether allergy includes immunity or is a process quite separate from immunity, whether the local fixation of bacillary antigen is or is not a function of allergy—these and numerous other matters are regarded in different ways by different investigators, and are all too frequently treated vaguely and even inconsistently.

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\* From the Department of Pathology, The Johns Hopkins University School of Medicine

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Although the term "allergy" signifies, broadly, a condition of altered reactivity, when applied to bacterial infections (and especially to tuberculosis) custom rather limits the use of the term to certain tissue reactions and constitutional symptoms which are quite different from those associated with anaphylaxis. This is a result of the work of Baldwin, Zinsser and others who have clearly shown that an animal may be highly anaphylactic to tuberculo-protein, falling into anaphylactic shock in the characteristic way when tuberculin is injected intravenously, and yet possess no capacity to exhibit a tuberculin reaction when tuberculo-protein is injected locally, and, conversely, an allergic animal, giving a brilliant local tuberculin reaction, may not be anaphylactic at all, although the intravenous injection of tuberculo-protein will cause grave symptoms, quite different, however, from those of anaphylactic shock. In this paper, therefore, anaphylaxis will not be included in the term "allergy."

Whatever the ultimate meaning and function of allergy may be, this much can be said with certainty. The infected body becomes changed in some manner which renders the relatively bland protein of the tubercle bacillus capable of acting on its tissues as a powerful irritant and poison. As a result of this change, the cells of the allergic body are more extensively damaged and killed by a given amount of tuberculo-protein than are the cells of the normal body, and, furthermore, because of this enhanced irritant action of tuberculo-protein on allergic tissues and because of the resulting more extensive damage and death of cells, there appears a more violent acute inflammation at the site of action of tuberculo-protein in the allergic body. More prompt and extensive damage and death of cells and more extensive acute inflammation constitute, therefore, the local visible expression of the action of allergy. Constitutionally, the greater irritative effect of tuberculo-protein on the allergic body is manifested by the fact that fever, malaise, prostration and death can ensue when an amount of tuberculo-protein which is harmless for the normal body finds its way into the blood stream of the allergic one. I think that it is important to realize clearly that everything which happens at the site of an uncomplicated allergic reaction is merely the standard reaction of the body to a chemical irritant. It is no curious or new type of reaction. With properly adjusted concentrations, it would be impossible to differentiate histologically between the site of a tuberculin reaction and a site into which one had injected sulphuric acid. I do not mean to imply here that tuberculo-protein itself acts as the irritant to the allergic tissues. Of that, one cannot yet speak with certainty. But it is certain that some substance, irritating and poisonous to the allergic body is present at the site of an allergic reaction, and I shall speak later of the nature of this irritant.

The more intense inflammatory response of the allergic body, as contrasted with the usual leisurely appearance of a tubercle following the introduction of bacilli into the tissues of the normal body, has led numerous competent investigators to believe that the allergic body has acquired, through infection, the capacity to react to the tubercle bacillus in a manner which is different qualitatively from that in which the normal body is able to react to that organism. One authority, for example, has recently written that when bacilli are introduced into the tissues of the normal body the development of a nodular tubercle is "the *only* anatomical response which such tissues will make," and that this response is not essentially modified by the numbers of bacilli introduced.

As for acute inflammation, the same writer has stated <sup>1</sup> "We never meet with inflammation in tuberculosis except in the allergic animal." In other words, the allergic body has acquired the power to react to the tubercle bacillus with acute inflammation—a power which the normal body did not possess.

I cannot share this view. The experimental studies which Dr McCordock and I have carried out leave no doubt in our minds that either the allergic or the normal body can respond to the bacillus with either tubercle formation or acute inflammation, and that the number of bacilli and their site of lodgment are of great importance in determining the character of the reaction. One or two bacilli deposited in certain tissues of even a highly allergic body may call forth only tubercle formation, on the other hand, while even moderate numbers of bacilli can call forth acute inflammation in the normal body, larger numbers always do. It is, however, clear that the acute inflammatory response of the allergic body to any given dose of bacilli will tend to be much more intense than that of the normal one. This is a result of the fact that, in addition to any inherent irritative property of the tubercle bacillus, tuberculo-protein acts as a far more powerful irritant in the hypersensitive body. Our most careful histologic studies have failed to reveal the slightest qualitative difference between the character of the local reaction of the normal and the allergic body to the tubercle bacillus, if such factors as time, the character of the infected tissue and the numbers of organisms are taken into account.

#### RELATION OF ALLERGY TO ACCELERATED TUBERCLE FORMATION

I have said nothing about "accelerated tubercle formation" as a part of allergy for the reason that, fundamentally, I do not believe that it is. In 1914, Rist and Rolland <sup>2</sup> observed that the injection of a small num-

<sup>1</sup> Krause. *Am Rev Tuberc* **15**:137, 1927.

<sup>2</sup> Rist and Rolland. *Ann de méd* **2** 13, 1914.

ber of tubercle bacilli into the skin of an allergic animal was followed, not by severe inflammation and necrosis, but by the development of a nodule, or tubercle, comparable to that formed in the skin of a normal animal as a response to a few bacilli. However, in the allergic animal this nodule developed somewhat more rapidly. Krause and Peters<sup>3</sup> confirmed this observation in a careful series of experiments, and the phenomenon has since become familiar to every observant student of the allergic reaction. It is this more rapid development of a tubercle in the allergic body that has come to be called "accelerated tubercle formation" and to be regarded as a form of the allergic reaction. At the risk of being regarded as attempting to erect distinctions that are not differences, I must draw into question the propriety of the universal acceptance of accelerated tubercle formation as an integral part of the allergic reaction, for although the phenomenon undoubtedly occurs as described, I believe that it is an accidental result of the allergic reaction rather than a part of it. In the Arthus phenomenon, in which nonbacterial proteins can serve as the antigen, and in every known example of bacterial allergy, the local tissue reaction is fundamentally the same, namely, damage to the cells, ordinary acute inflammation and, if the dose of antigen is large enough, death of the cells. It is true that the rapidity and the intensity with which these effects follow the application of the antigen are different in different cases. In some instances, furthermore, the acute inflammatory exudate will be predominantly serous, while in others it will be purulent, perhaps. The cells of the exudate may vary in type, the tissue cells may be merely irritated, they may be damaged, or they may be killed outright. But there seems to be a single fundamental mechanism underlying allergic tissue reactions, no matter what the antigen may be, and, no matter what the antigen, the tissue reaction is always fundamentally the same, that is, the standard reaction of the body to a chemical irritant. It therefore clouds somewhat, the concept of allergy if one gathers into the term everything that happens when the hypersensitive body is exposed to the complex body of the tubercle bacillus. It is known that the allergic reaction is called forth by the protein part of the bacillus, and that when tuberculo-protein alone is injected into the allergic body cellular damage, necrosis and inflammation result, but never tubercle formation. It is well known that tubercle formation is a result of the presence not of soluble tuberculo-protein, but of the lipid part of the bacillus. None of the lipid is needed to elicit the allergic reaction, nor can one produce the allergic reaction by injecting the lipid alone into the allergic body. If, however the lipid happens to be present by the side of tuberculo-protein, wandering cells attracted rapidly to the spot by the action of the protein will engulf the lipid

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3 Krause and Peters. *Am Rev Tuberc* 4 551, 1920

and form tubercles. It is extremely probable, although I have never attempted to demonstrate it, that any nonspecific foreign body tubercle would be formed with greater rapidity if the inert particulate matter were injected together with an inflammatory irritant, and this merely because the wandering cells would be more rapidly attracted to the spot. But it is in no sense justifiable to confuse the process of acute inflammation with that of tubercle formation. Acute inflammation is a complicated, specific type of reaction, and tubercle formation is a separate, different process. Acute inflammation involves primarily a vascular reaction and does not imply any tendency to the formation of tubercles. On the other hand, the tubercle requires no inflammatory vascular paralysis for its evolution. It is, phylogenetically, the most primitive organized form of reaction to invading organisms, and occurs in lower animals which possess no circulatory system and in which, therefore, acute inflammation is out of the question. Tubercles can be formed independently of blood vessels in any tissue in which mononuclear phagocytes are present and, indeed, even *in vitro* on a coverslip in tissue cultures. Since, in tuberculosis, they are a response only to the lipoid of the bacillus and since that lipoid cannot itself elicit the allergic reaction, one must regard accelerated tubercle formation as merely an accidental complication of the presence of the lipoid at the site of action of tuberculo-protein, and not as a specific type of expression of the allergic mechanism.

The objection which I have raised is not an idle or scholastic one. It is made in the attempt to remove, as far as possible, all extraneous and confusing matters from the concept of bacterial allergy, and to emphasize the fact that local hypersensitive reactions to protein are, in essence, all alike, regardless of what protein serves as the antigen. They are all alike in that they all consist in irritation, damage, or death of cells, and in ordinary acute inflammation. At the least, I would urge a thorough and separate inquiry into the mechanism of every additional phenomenon which may be observed to happen in association with allergy before it is complacently regarded as an integral part of the allergic mechanism.<sup>4</sup>

#### RELATION OF ALLERGY TO LOCAL FIXATION OF BACILLI

From such a standpoint, let us examine the relation of allergy to the alleged local fixation of tubercle bacilli in the immune body. Since the

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4 From this point of view, it is clear that the present tendency to speak glibly of the lesions of rheumatic fever as "allergic manifestations" of infection with a streptococcus may justly be regarded with suspicion. While it is always possible that the acute inflammatory lesions in this disease may be associated with allergy, the specific Aschoff body is a completely different sort of reaction and should, for that reason, even if one is willing to ignore its astonishing specificity, point to the presence of some, as yet undiscovered, specific etiologic agent at the site, capable of producing a lesion of the character of the Aschoff body.



early studies of Koch, innumerable experimental observations have suggested that the spread of viable bacilli from a local focus of reinfection is interfered with in some way in the immune body. Krause and Willis<sup>5</sup> have made an especially careful study of this matter. Their method, briefly, was this. A measured number of virulent bacilli were injected into the skin of normal animals and of animals which had been previously made immune by an injection of bacilli of low virulence. At frequent intervals following the introduction of the virulent bacilli into the skin, the lymph nodes draining the sites of cutaneous infection were excised, and inoculated into fresh animals, in order to find out whether or not they contained tubercle bacilli, and thus to determine whether, in the immune animals, there had been any delay in the escape of the bacilli from the cutaneous site of inoculation. These authors found that the nodes taken from the normal, nonimmune animals contained living bacilli as early as twenty-four hours after the injection into the skin, but the nodes draining the infected skin areas of the immune animals were not infective before the end of two weeks after the cutaneous inoculation. Their conclusion was, therefore, that when tubercle bacilli enter the tissues of an immune animal they are held fixed at the site where they lodge for a considerable length of time, and then spread throughout the body in correspondingly delayed, as contrasted with the rapid spread of the bacilli in the nonimmune animal. This is what is meant by the term "local fixation" of bacilli. While it is entirely possible, especially in the light of Opie's work on nonbacterial antigens, that many kinds of bacteria may be held fixed at the site of their entry into the immune body by some specific mechanism, so far the results of methods which have been designed to demonstrate bacterial fixation are susceptible of other possible interpretations. It must be remembered, for example, that tubercle bacilli cannot live as well, and are more rapidly destroyed in the immune body, it is therefore possible that they were not held fixed, bodily, in the skin in the foregoing experiments, but that the early lack of infectivity of the regional nodes of the immune animals was a result rather of the fact that there were too few viable bacilli within those nodes when they are excised. Certainly, we ourselves have never been able to discover any difference between the number of stainable bacilli at the site of inoculation into the skins of normal and immune animals during the first few days after the inoculation, and after that, the number of bacilli in the area in the normal animals surpasses that in the immune animals—quite the reverse of what one would expect to find if the bacilli were quickly drained from the site in the normal animals, and actually held there bodily for days in the immune animals. While there are objections to conclusions drawn

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5 Krause and Willis. *Tubercle* 6 438, 1925

from the number of stainable bacilli in such experiments, there are also certain rather grave sources of error in the experiments designed to demonstrate the fixation of intact bacilli, and undoubtedly more work of a different nature must be done to settle the question. However, if one provisionally accepts the view that the bacilli are actually held fast, bodily, in immune tissues, how is this immobilization effected? In the immune body, allergy is usually present also, and consequently a more marked inflammatory reaction follows the introduction of bacilli, and it is to this allergic inflammatory reaction that the immobilization of the bacilli has been attributed by numerous writers. The inflammatory exudate has been assumed to hold the bacilli mechanically at the spot and so to prevent their spread, and this is one of the reasons why allergy has been regarded as a mechanism of immunity. I cannot discuss here the various facts which speak against the view that acute inflammation per se can prevent, so immediately and completely, the spread of bacteria. Such a discussion would lead us into the problem of why certain bacteria have an innate tendency to grow in localized colonies in the tissues of the normal body, while other bacteria tend to spread rapidly and diffusely through the tissues in spite of the most intense inflammation. It would also be necessary to consider the fact that inert particles, red cells, fragments of cells and phagocytes laden with debris are drained freely and in abundance from an area of acute inflammation, as the most cursory examination of the sinuses of regional lymph nodes will show, and, further, that the lymph drainage from a site of acute inflammation is more abundant than from the same area in its normal state. These and numerous other facts, difficult to reconcile with the alleged power of an acute inflammatory exudate to stop at once the spread of bacteria through the lymphatics, have been discussed at length in another place.<sup>6</sup> I can only say now that if the bacilli are actually held fixed in the immune body at the site of reinfection, it is much more probable that they are so held not by inflammatory exudate, but by some specific, precipitin-like mechanism such as that suggested by Opie to explain the local fixation of foreign protein, such as egg white, when introduced into the tissues of the sensitized body. Discussing the rôle of specific precipitation in the local fixation of protein antigens, Opie writes that, in the sensitized body, "the foreign substance, fixed at the site of injection, produces here an intense reaction."<sup>7</sup> I interpret that to mean that he regards the intense inflammatory reaction rather as a result of the local fixation and maintenance of local concentration of the antigen—quite the reverse from the view of Krause and others who maintain that it is the inflammatory reaction which

6 Rich and McCordock. *Bull. Johns Hopkins Hosp.*, 1929, to be published.

7 Opie. *Tubercle* 7 23, 1925.

holds the antigen fixed at the spot. I would, further, call attention to the fact that, without exception, all those who assume that it is acute inflammation which holds the bacilli fixed mechanically nevertheless admit the undeniable fact that when acute inflammation occurs about a quiescent tuberculous focus, there is a pronounced tendency, not to the immobilization of the bacilli at that site, but to their spread from it, and, as far as I can find, no attempt is made to reconcile this fact with the assumption that a severe acute inflammation can prevent the immediate spread of bacilli.

I shall not dwell further on this question except to say that there is at present no reason that I know for regarding the local fixation of bacilli as a part of the allergic reaction and, until more is learned about the matter, I believe that it is wiser to regard the two phenomena as separate and dissociable, and to try to analyze separately the underlying mechanism responsible for the immobilization of the antigen when such immobilization occurs, and that responsible for the allergic hypersensitivity of the tissues to the antigen in question.

#### THE MECHANISM OF ALLERGY

It is obviously of prime importance to try to understand the underlying mechanism of allergic hypersensitivity—the mechanism responsible for the fact that the tissues of the infected body are readily injured and killed by the introduction of amounts of tuberculo-protein which are relatively harmless to the tissues of the normal body. Since the actual substance introduced is the same in each case, it is clear that the allergic body has become changed in such a way that either tuberculo-protein itself now can act directly on it as a powerful irritant and poison, or else that the body has acquired the power to act on tuberculo-protein with the resulting formation of a noxious substance, which then damages the cells. Both the cellular damage and the inflammation of the allergic reaction are, as I have said, merely the manifestations of the action of an irritant to which the allergic body is susceptible. What is the explanation of this fact that tuberculo-protein is a violently irritating poison to the tissues of the allergic body?

In the light of what is known of protein hypersensitive reactions it is generally believed that the most probable explanation of the allergic cellular damage and inflammation in tuberculosis is that they are the results of an antibody-antigen reaction, in which tuberculo-protein constitutes the antigen which reacts with an antibody formed during infection. According to this view, the cells of the sensitized body might be unchanged and normal, while the plasma and tissue fluids contained the antibody capable of acting on tuberculo-protein to yield an irritating substance, toxic for the normal cells. If this were so, the addition of tuberculo-protein to the plasma of an allergic animal should result in

the formation of a toxic substance that would cause cellular damage and inflammation in any animal, whether allergic or not. In spite of the fact that passive transfer of allergic hypersensitivity to tuberculin has been doubtful, or at least difficult and irregular, there were reports in the literature indicating that this might be the basic mechanism of allergy, therefore, several years ago we tested the possibility at some length by incubating tuberculin in various ways with plasma from allergic animals, and then injecting the mixtures into normal animals, in order to determine whether or not injurious substances had been formed as a result of the contact of tuberculoprotein with allergic plasma. We were never able to produce anything comparable to tuberculin reactions by the injection of such mixtures into the normal animal. Zinsser, likewise, recently reported similar negative results.

A second possibility to be considered is that the active antibody does not circulate freely in the body fluids, but that it is bound to the tissue cells in such a way that the antigen-antibody reaction leading to the formation of the injurious substance takes place actually within or on the cells. Zinsser feels that he has obtained some evidence that this is the case by means of injecting mixtures of tuberculin and extracts of ground up tuberculosis tissue into the skin of normal animals, but he speaks of his positive results as "irregular and occasional" <sup>8</sup>

Finally, it is conceivable that the production of cellular damage through allergic hypersensitivity is a result of an antibody-antigen reaction dependent on alterations in both the tissue cells and the body fluids.

For numerous reasons, into a discussion of which I cannot enter here, it was felt that experiments of the nature of those I have mentioned left much to be desired in the matter of proving or disproving the site of antibody localization, and, since it had never been proved whether or not the individual cells of the allergic body are themselves inherently changed in any manner which renders them more susceptible than normal cells to the protein of the tubercle bacillus, Mrs. Lewis and I <sup>9</sup> recently applied ourselves to the attempt to answer the following direct question: Is it true that, following infection with the tubercle bacillus, the individual cells of the various tissues of the body do become changed in such a way that they are more readily injured by tuberculoprotein, regardless of the character of the body fluids by which they are surrounded?

In order to answer this question, it is necessary to be able to compare by direct observation the effect of tuberculoprotein on the isolated, living cells of normal and of allergic animals, and the method naturally chosen was that of tissue culture. Only in this manner can cells be

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<sup>8</sup> Zinsser. *J. Exper. Med.* **44** 753, 1926.

<sup>9</sup> Rich and Lewis. *Proc. Soc. Exper. Biol. & Med.* **25** 596, 1928.

kept alive for days, separated from their own body fluids, and removed from the complicating effects of circulatory, metabolic and nervous influences, and from the uncontrollable variations in antigen concentration which may result from the local fixation of the antigen. It is hardly necessary to recall how decisive was the *in vitro* method when it was applied to the solution of the mechanism of anaphylaxis.

It is clear that, if the bodily change underlying the allergic state is primarily a cellular one, the tissue cells when removed from the allergic body will exhibit a greater susceptibility to tuberculin even when surrounded by plasma from a normal animal. If, on the other hand, there is an antibody in allergic plasma which can react with tuberculin to produce an injurious substance analogous to anaphylatoxin, normal cells should be visibly injured when grown in such a medium, for tissue culture provides a delicate method of studying the effects of injurious substances on cells. Finally, if both a cellular change and a circulating antibody are necessary for the reaction, allergic cells should be injured when exposed to tuberculin in the presence of allergic plasma, but uninjured by tuberculin in the presence of normal plasma. These were the possibilities which we had before us at the outset.

Briefly, our technic was to wash thoroughly, through several changes of Locke's solution, the minute fragments of tissue which were to be used for the cultures, in order to free them as completely as possible from any adherent tissue fluids. The pieces of tissue were then placed in plasma to which tuberculin had just been added in the desired concentration. In each experiment we used cells and plasma from a normal guinea-pig, and from an allergic guinea-pig which had reacted strongly to tuberculin intracutaneously before the experiment. The cells used were white blood cells from the buffy coat of centrifugalized blood, and also the tissue of the splenic pulp, which grows readily in culture. Old tuberculin, water extract and broth filtrates of cultures of tubercle bacilli were used as antigen. As a control, the standard concentrated glycerin broth control for old tuberculin was used. This control was always entirely harmless to both normal and allergic cells in the concentrations used to control the effect of the tuberculin.

The results of these experiments, which were sharp and clear-cut throughout a series of many hundreds of cultures, demonstrated that, during infection, the individual tissue cells actually become altered internally in some manner which renders them inherently more susceptible to tuberculin than they were before. Allergy, therefore, resides in the cells, and not in the body fluids. At least, no circulating antibodies are necessary for the production of the injurious local effects of allergy in tuberculosis. This is in agreement with the fact that the results of attempts to transfer tuberculin allergy passively have always been doubtful. The intimate nature of this cellular alteration remains to be solved. It cannot yet be stated with certainty that an antibody-antigen reaction takes place, but it is extremely probable that such is the case. One of the most curious circumstances relating to the problem is the

well known fact that although the allergic body is hypersensitive to tuberculo-protein extracted from the bacillus, this hypersensitiveness cannot be induced by the injection of tuberculo-protein. Whole bacilli, alive or dead, must be injected in order to set up the allergic state. Perhaps this is only because the artificial injections of tuberculo-protein have not fulfilled the conditions of its liberation and absorption during infection, or perhaps the true sensitizing antigen is not the extractable tuberculo-protein, but a parent substance present in the body of the bacillus and changed during extraction.

#### THE INFLUENCE OF ALLERGY ON THE CHARACTER OF LESIONS

I shall turn now to the rôle that allergy plays in determining the type of lesion which the tubercle bacillus will produce. The extent and character of any given tuberculous lesion found at autopsy have been determined by the interplay of a number of factors, chief among which are the virulence and the numbers of the infecting bacilli, the degree of native, individual and acquired resistance of the body, the degree to which allergy is developed, the character of the tissue in which the bacilli lodge, and the length of time which has elapsed since the bacilli were deposited at the site in question. Obviously, most of these factors are completely lost to one in any given case of human tuberculosis which comes under observation, but they can, for the most part, be governed or measured in the experimental animal. Dr McCordock and I<sup>6</sup> have accordingly made a comprehensive study of the results of the interplay of these factors under controlled conditions. From such a study we have become able to interpret the manifold types of tuberculous lesions with a feeling of much greater security in the correctness of our interpretations than we formerly had. I cannot enter here into the general results of this investigation, but I would say that there are a number of rather simple principles governing the influence of the previously mentioned factors on the character of the lesion, and that the application of these principles allows us to forecast the effect of various experimental combinations and, therefore, to reconstruct, with better understanding, what has happened at the site of the lesions encountered in human autopsy material. As an example of the manner in which the application of these principles can further the understanding of certain types of lesions, let us consider for a moment the lesion characteristic of acute caseating miliary tuberculosis. It has long been known that when a sufficiently large number of unselected cases of miliary tuberculosis are studied microscopically, they can be divided into two groups. First, there are the cases in which true tubercles are scattered through the tissues—tubercles of the textbook variety made up of compact aggregations of well preserved epithelioid cells and giant cells bound together by reticu-

lum For convenience I shall call these "hard" tubercles, in contrast to the second type in which the scattered tubercles are loosely formed, and the cells composing them exhibit a marked tendency to undergo early death, so that even the most minute aggregations of cells frequently appear as small foci of caseation. The latter type I shall refer to as the "soft" tubercle. There has been not a little speculation concerning the reason for the existence of these two types of miliary tubercles. Some have thought that bacilli of different degrees of virulence might be the underlying cause of the difference in rapidity and extent of necrosis, others have regarded the soft type as an evidence of "low resistance" on the part of the body, recently, the view has been advanced that the small caseous foci are merely the very early stage of the larger hard tubercles, with central caseation. However, none of these views will stand the test of critical examination. Since the striking difference between the hard and the soft tubercle is the tendency to rapid necrosis of the cells of the soft variety, it should suggest itself at once that allergy is involved in the matter, for it is allergy which, in effect, transforms tuberculo-protein into a necrotizing poison. Can one say, therefore, that the presence of a high degree of allergy is the cause of the necrosis of the soft tubercle? Not at all. We have repeatedly found fresh, well preserved, hard tubercles in patients and animals in which allergy was at a high level at all times during the several weeks before death, as determined by repeated, graded tuberculin tests. It is at this point that one may make use of one of the simplest and most obvious of the principles relating to the effect of allergy on a lesion—namely, the principle that one or two bacilli are not sufficient to cause necrosis of any extent, even in the face of an extreme degree of allergy. That must be familiar to every one, for every one knows that a minute amount of tuberculin, such as could be obtained from one or two bacilli, would not cause a sloughing tuberculin reaction, but it was not until we deliberately applied to the question the obvious fact that both allergy and numerous bacilli are required for rapid and marked necrosis that we were able to understand the nature of the soft tubercle. Then, the injection of graded doses of bacilli into allergic and normal animals, as well as the comparison between the numbers of bacilli in hard and soft tubercles in man, soon made it clear that the soft tubercle was merely the result of the presence of large numbers of bacilli acting in the face of allergy. The difference in the number of bacilli to be found in the hard and soft types of tubercle is enormous.

This leads one to certain matters of interest from the standpoint of symptomatology. McCordock and I<sup>6</sup> have, in another place, offered what we believe to be very good evidence against the old view that miliary

tuberculosis is always the result of a sudden discharge of quantities of bacilli into a large vessel, and in favor of the view that many cases result from a much more gradual infection of the blood stream through microscopic vessels. In the case of the soft tubercle, however, one does find in the tissues exactly what might be expected as a result of the sudden discharge of large numbers of clumped bacilli from a caseous focus into the blood stream. Indeed, in a human case in which autopsy was performed at a very early stage of the process, such clumps were actually found in the capillaries of various tissues. It is well known that when a large number of bacilli or caseous debris impregnated with tuberculo-protein is suddenly injected into the blood stream of an allergic animal, that animal quickly develops a constitutional allergic reaction and becomes very ill. One should, therefore, expect that, in man, in the instances in which miliary tuberculosis is caused by the sudden discharge of a caseous focus into a large vessel, the accident should be heralded by a sudden, severe onset of illness, with symptoms of a constitutional tuberculin reaction, whereas, in the instances in which miliary tuberculosis arises as a result of the gradual feeding of bacilli into the blood stream, the onset should be insidious. As a matter of fact, the development of the great majority of cases of miliary tuberculosis is so gradual that the onset cannot be determined clinically, and in the great majority of cases hard tubercles containing very few bacilli are found in the tissues at autopsy. On the other hand, in reviewing the clinical histories of our cases of miliary tuberculosis in which soft tubercles were found, in each instance there was a story of a sudden, stormy onset leading to death. The sudden discharge of a caseous focus into a large vessel in an allergic individual may thus be recognized clinically by the abrupt onset of symptoms, and pathologically by the presence of soft tubercles in the tissues at autopsy.

I should like to cite another of the numerous instances in which the application of principles derived from experiments has led to a clearer understanding of the lesions produced by the tubercle bacillus. What is the pathogenesis of tuberculous meningitis? If one turns for information to the leading textbooks and to the literature, it will be found that while it is mentioned that meningitis may in rare cases result from the extension of tuberculous infection from a focus situated within the brain or within the bones that enclose the central nervous system, most cases are regarded as the prompt result of direct meningeal infection by way of the blood stream, appearing usually as a part of the widespread dissemination of bacilli during the septicemia responsible for miliary tuberculosis. This belief is, without doubt, a result of the frequent coincidence of miliary tuberculosis and tuberculous meningitis, especially in children, together with the fact that



the demonstration of an older adjacent tuberculous focus as the source of the meningeal infection has been decidedly exceptional in any routine series of cases. What, now, is the usual character of the meningeal reaction? A moment's thought of the extensive inflammatory exudate and of the widespread necrosis of the inflammatory cells and the contiguous meningeal tissues will leave no doubt in one's mind that acute tuberculous meningitis represents a model example of the allergic inflammatory-necrotizing reaction. If one applies the same simple principle which has just been invoked in the explanation of the soft tubercle, it will be realized that the violent allergic reaction observed in the meninges cannot have been produced by only a few bacilli. A great many must escape into the meningeal spaces to initiate such an allergic response. Now it is universally observed without hesitation that tubercle bacilli circulating in the blood during the course of milary tuberculosis can readily lodge in the meninges in numbers sufficient to call forth the inflammatory necrotizing reaction. There were, however, several considerations which stimulated us to test the validity of this assumption. In the first place, we had become familiar with extreme forms of milary tuberculosis in which, in spite of the fact that every susceptible organ was riddled with tubercles, there was no meningitis at all, not even in cases in which we knew that allergy had remained at a high level up to the time of death. Why had these allergic patients not developed meningitis if circulating tubercle bacilli readily settle out in the meninges in large numbers? In the second place, a careful study of our cases of tuberculous meningitis associated with milary tuberculosis soon convinced us that the lesion in the meninges is by no means always of the same age as the tubercles scattered through the viscera. There were even cases in which the visceral milary tubercles were unquestionably younger than the meningitis. Again, there were in our records the rather baffling cases in which meningitis existed in the complete absence of milary tuberculosis and also in the absence of any discovered local tuberculous focus from which the infection could have extended. The literature has shown us that the records of our department are not unique in the experience of cases of this sort. Finally, we had never observed the development of meningitis as a direct result of the large number of experimental intravascular injections of tubercle bacilli which we had carried out for other purposes.

We therefore set about in the deliberate attempt to produce tuberculous meningitis by repeated injections of large numbers of virulent bacilli into the circulation of allergic animals. We were entirely unable to produce meningitis by this means even when we injected clumps of bacilli directly into the carotid artery. At best there appeared here and there a few scattered tubercles in the meninges although the

viscera in such experimental animals were studded with tubercles. It soon became clear to us that, in the guinea-pig, rabbit and dog, tubercle bacilli circulating in the blood do not tend to lodge in large numbers in the meninges. The amount of tuberculosis found in any tissue following infection by the blood stream undoubtedly is determined partly by the ability of that tissue to stop and hold any circulating foreign particulate matter, and the experiments of Brickner<sup>10</sup> in our laboratory have demonstrated that the meninges belong to the group of tissues which stop and hold only minute amounts of circulating particulate matter. We have found the same to be unquestionably true of circulating tubercle bacilli, and the presence of allergy does not increase the ability of the meninges to stop the bacilli. Tuberculous meningitis, then, cannot be produced as a direct result of blood stream infection in animals, and the cases of extreme miliary tuberculosis without meningitis indicate clearly that the same is true of man, for it is a fact that the relative degree of involvement of different tissues in miliary tuberculosis in man is always the same. It never happens, for example, that the spleen or the lungs are spared in a case in which the other susceptible organs are full of miliary tubercles. The fact that the meninges are not infrequently spared in such cases means only that they are never heavily infected directly from the blood.

Although we could not experimentally produce meningitis by sending tubercle bacilli to the meninges by way of the blood stream, it was, however, easy to set up typical tuberculous meningitis by the injection of bacilli directly into the subarachnoid space of allergic animals, thus fulfilling the conditions of the principle that, for the production of extensive allergic reactions, large numbers of bacilli are required.

It is evident that all these considerations made us hesitate to share the generally accepted view that, during the septicemia of miliary tuberculosis, bacilli lodge in the meninges from the blood stream in numbers sufficient to call forth the acute diffuse allergic reaction characteristic of tuberculous meningitis. Where, then, were the bacilli coming from, if not directly from the blood stream? The only other possibility was that the meninges were being directly infected by the discharge of bacilli into them from some adjacent tuberculous lesion. We therefore began to examine minutely the human material at our disposal and, by laboriously cutting the brains into very thin slices and by keeping a sharp lookout for caseous lesions, older than the meningitis, in communication with the meninges or the ventricular cavities, we found to our surprise that we were able to demonstrate such lesions in almost every case in which we had the entire central nervous system for examination. Small caseous tubercles in the cortex, although rarely numerous, are

10 Brickner Bull. Johns Hopkins Hosp. 40:90, 1927.

frequently present in cases in which there is a progressive visceral tuberculous lesion of any extent, even in the absence of miliary tuberculosis, for periods of mild bacillema, with consequent dissemination of bacilli, are the invariable accompaniment of progressive lesions. Similar discrete, sparsely scattered tubercles may be found in the meninges, though more rarely than in the substance of the brain. For the production of meningitis, it is necessary only that these meningeal or cortical tubercles grow, caseate and discharge their bacilli into the meninges. Without such extension from the brain, meninges, or surrounding bones we believe that tuberculous meningitis will never occur, and we have been able to demonstrate such discharging lesions, usually multiple, in 90 per cent of the forty cases of meningitis we have studied. In the four cases in which the site of discharge was not found, we did not have the entire brain or the middle ears for examination. It must be remembered that the tubercle bacillus differs from pyogenic organisms in the important fact that it cannot multiply so rapidly. One or two pyogenic bacteria escaping into the meninges will have formed colonies within twenty-four hours, but not so with the tubercle bacillus. In the infected, immunized body one or two bacilli lodging at any site will either be killed outright or else encapsulated. Of course, not every tubercle which extends to the meninges will set up meningitis. Many of them are completely encapsulated, and this is especially true of large tubercles in the brain.

I cannot now enter into the other proofs of the correctness of this view of the pathogenesis of tuberculous meningitis which have been brought together elsewhere,<sup>11</sup> or do more than mention that the same principle of direct extension of infection from an adjacent lesion governs the development of tuberculous inflammatory effusions into any serous cavity. Such serous effusions are never the immediate result of blood stream infection of a serous cavity. I have offered this revision of our own attitude on the question of tuberculous meningitis only as an example of the manner in which the various principles relating to allergy, which have been established by experiment, may be applied to the clearer understanding of the pathogenesis of the most diverse forms of tuberculous lesions.

#### RELATION OF ALLERGY TO ACQUIRED IMMUNITY

Throughout this discussion of allergy, the effects of allergic hypersensitivity to tuberculo-protein have been repeatedly referred to in terms of tissue damage and destruction, and untoward constitutional symptoms. However, since it was learned long ago that the specific, inherited, coordinated reactions of the body usually serve the purposes of protection and survival, it is only natural to feel that the complicated

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11 Rich and McCordock. To be published, Bull. Johns Hopkins Hosp.

mechanism of allergy must also exist for some serviceable end. That allergy is an agent of tissue injury—that, indeed, the only thing which is really known about the result of the action of allergy to tuberculo-protein is that it produces tissue damage—is perfectly true. But it is hardly possible to believe that acquired tissue hypersensitivity to protein is, in essence, a mechanism contrived for the survival of bacteria at the expense of the animal host. Indeed, so far from believing any such thing, the vast majority of investigators today hold the belief that the allergic state is a direct mechanism of defense against the invading micro-organism. Although it is so widely accepted as a fact, I cannot emphasize too strongly that the concept of allergy as a necessary mechanism of immunity to bacterial infection is still purely in the stage of hypothesis. To discuss the matter adequately would require more time than the bounds of this lecture permit, but I must speak about the question, however incompletely, for the problem of the exact status of allergy in relation to immunity is one of the most important matters concerned in the pathogenesis of tuberculosis. Every observant student of the disease knows well that extensive tissue destruction and constitutional symptoms are directly dependent on allergic hypersensitiveness to tuberculo-protein. It is therefore of fundamental importance not only for theoretical but also, perhaps, for practical reasons to know whether or not this hypersensitive state which, in effect, converts the bland protein of the bacillus into a most violent poison, is necessary in any way for the operation of acquired immunity.

The hypothesis that allergy is a mechanism of immunity rests, largely, on the fact that, following infection, both allergy and immunity appear about the same time and are usually coexistent thereafter. The more prompt and intense inflammatory reaction which follows the introduction of numbers of bacilli into allergic tissues has led to the belief that it is through this reaction that the bacilli are killed and prevented from spreading. In the instances in which only a few bacilli are introduced into the allergic body and no marked inflammation results, but instead a somewhat more rapid evolution of a tubercle, this more rapid encapsulation of the organisms is interpreted as a mechanism of immunity in that it, too, prevents the spread of the bacilli throughout the body. The destruction of tissue through the agency of allergy is regarded, from this point of view, as a local sacrifice, necessary for the survival of the body as a whole. In view of the unusually destructive nature of hypersensitiveness in tuberculosis, it is important to know whether or not this local sacrifice of tissue is actually necessary for the operation of immunity.

I have already pointed out that there are reasons for believing that it is not the inflammation of allergy which prevents the spread of the

bacilli As for the great emphasis which is laid on accelerated tubercle formation as a mechanism of immunity, while it is clear that this process tends to aid mechanically in the prevention of spread of the particular bacilli enclosed in each tubercle, I believe, nevertheless, that accelerated tubercle formation is neither a necessary nor a decisive factor in acquired resistance. It is well known that mere phagocytosis and the formation of a tubercle about bacilli is not sufficient, alone, to prevent their multiplication, or else progressive infection would not even follow the intravenous injection of bacilli into the nonimmune body, for within a short time after such an injection, all of the bacilli are within phagocytic cells, and tubercle formation is well under way. Indeed, the clearest way to become convinced that the mere prevention of spread of bacilli is of little consequence in itself is to observe what happens in the immune animal after the organisms are deliberately spread throughout every tissue by the injection of a fine suspension of bacilli directly into the blood stream. Several weeks later, at autopsy, these immune animals will show few lesions, while nonimmune controls which received the same dose at the same time will have developed widespread tuberculosis, with myriads of tubercles throughout their tissues. If the suspension of bacilli is fine enough and a very small dose impacted so that single bacilli stop here and there, no appreciable allergic inflammation occurs in the tissues, and indeed, the difference in the rapidity of tubercle formation in the immune and the control animals will be truly negligible, yet the bacilli thrive in the nonimmune animals but fail to proliferate freely and die out in the immune ones, urging attention to the fact that the immune body is a poor medium for the bacillus, regardless of the allergic reaction.

What now of the idea that it is the more rapid and extensive allergic inflammation which kills the bacilli more promptly in the immune body? What I have just said indicates that, in the immune body, there must at least be some other mechanism unfavorable to the life of the bacillus, but can the allergic inflammation serve that purpose also? If it could be shown that the circulating blood of the immune body possessed potent bactericidal, lytic or growth inhibiting properties, it would be clear that it would be beneficial to have those antibodies brought quickly by inflammation to any site at which the bacilli lodge. However, up to the present, the most painstaking efforts by others as well as by ourselves have consistently failed to demonstrate that the plasma of immune animals possesses any greater power of destroying or inhibiting the growth of the bacilli than the plasma of susceptible, nonimmune animals. What then of the cellular portion of the inflammatory exudate? It is generally agreed, I believe, that in the normal body the polymorphonuclear leukocyte plays little rôle in the destruction of the

tubercle bacillus The only prominent phagocytic defense which the body possesses against this bacillus is the mononuclear phagocyte, and the merest novice soon learns that the bacilli can live and multiply only too well within these cells in the normal animal It is conceivable, however, that in the immune body these phagocytes have acquired a greater power of digesting the bacillus Mrs Lewis and I have, therefore, for some time been engaged in feeding tubercle bacilli *in vitro* to polymorphonuclear and mononuclear phagocytes taken from immune and from normal animals, but so far we have not been able to detect the slightest difference between the digestive powers of the phagocytes taken from the immune animals and those taken from the nonimmune animals Thus, in spite of the fact that the survival and growth of the bacillus are greatly hampered in the intact, immune body, up to the present neither the fluid nor the cellular part of the blood of the immune body has been found to possess anything definitely injurious to the tubercle bacillus *in vitro* which does not exist in normal blood It is therefore difficult to believe that the bringing of the blood by inflammation to the site of localization of bacilli can be the secret of immunity, and, as a matter of fact, Krause and Willis<sup>12</sup> have shown that the injection of bacilli into sites of prepared, acute, allergic inflammation in the immune body not only fails to bring about a more rapid destruction of the bacilli, but actually favors infection, as compared with the results of injecting the same number of bacilli into a noninflamed area I have already mentioned the decidedly unfavorable effect of acute inflammation on latent foci of bacilli

It is important for the present discussion that allergy and immunity do not always parallel each other in intensity Thus, Petroff and Stewart<sup>13</sup> have recently shown that the allergy established by the proper injection of dead bacilli is in no respect distinguishable in intensity from that resulting from infection with living bacilli, yet the immunity acquired from the injection of dead bacilli is distinctly less than that following infection with living organisms Furthermore, Willis<sup>14</sup> has shown that allergy wanes and practically disappears after the lapse of months following an immunizing infection, but the animals in which allergy is virtually absent are nevertheless found to be highly immune when inoculated with virulent bacilli Such experiments as these are among the observations which indicate that allergy and immunity may be separable, dissociable phenomena and that the degree of immunity may not depend on the degree of allergy

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12 Krause and Willis *Am Rev Tuberc* **4** 563, 1920

13 Petroff and Stewart *J Immunol* **12** 97, 1926

14 Willis *Am Rev Tuberc* **17** 240, 1928

These experiments of Krause, of Petroff and Stewart and of Willis, although they appear to me to speak against the identity of allergy and immunity, are nevertheless the products of investigators who adhere to the view that allergy is essential for immunity. I regret that I have not sufficient time now to discuss the explanations which the respective investigators offer for these results, for they are results which are not entirely consistent with their own point of view.

The experiments which I have just cited, and also numerous other facts relating to other infections as well as to tuberculosis, must at least render one hesitant about accepting too readily the current statements about the necessity of allergy for the operation of acquired immunity, and should urge us to search further for a different and more fundamental mechanism of immunity. Even if the blood of the body with acquired resistance could be shown to possess acquired bactericidal powers, it is clear that the allergic inflammation, by bringing that blood rapidly to a spot, would only be serving as an assistant to the separate, acquired, bactericidal mechanism of immunity. It is customary, of course, to think of acquired immunity in terms of specific bactericidal antibodies, chiefly because such antibodies do play an important rôle in the acquired immunity to certain micro-organisms. It is, however, not impossible that in tuberculosis and in certain other infections the mechanism of acquired immunity consists, not in the acquisition of specific bactericidal properties, but in some more subtle incompatibility between bacterium and host which interferes with free parasitism. If such were the case, there is no reason to believe that the inflammation of allergy would in any way serve that incompatibility. That a special tendency to exudative inflammation is completely unnecessary for the successful operation of an immunity of the latter type must be obvious from the fact, observed by Lewis and Sanderson<sup>15</sup> as well as by ourselves, that the reaction of the normal rabbit to virulent human tubercle bacilli is as slow and leisurely and as proliferative in character as is that animal's reaction to virulent bovine bacilli, yet the latter infection progresses to a fatal termination, whereas the former is completely resisted and does not. The same is true of the reaction of the guinea-pig to the  $R_1$  human bacillus of low virulence, as compared with this animal's reaction to a virulent strain. The lack of a difference in the histologic response of the tissues of the rabbit to the two forms of bacillus is somewhat difficult to link with the recent report of Lurie<sup>16</sup> that during the first few days after infection the human type of bacillus proliferates much more rapidly in the tissues of the rabbit than does the bovine type. The ultimate correlation of these observations will be of considerable interest.

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15 Lewis and Sanderson. *J Exper Med* 45 291, 1927.

16 Lurie. *J Exper Med* 48 155, 1928.

Meanwhile, there is not the slightest evidence that the phagocytes or the fluids of the rabbit are able specifically to destroy a virulent human bacillus more easily than a virulent bovine one, or that the guinea-pig has a more efficient specific bactericidal defense against a strain of low virulence than against one of high virulence. Since whether progressive infection will or will not occur in any case depends entirely on whether or not the bacilli can proliferate freely in the body in question, the most that can be said is that the growth requirements of different types and strains of tubercle bacilli must be different, and that natural immunity may often depend entirely on whether or not a given animal body is able to satisfy those requirements. In the case of acquired resistance to the tubercle bacillus, the evidence at hand suggests, at least, that there has occurred in the resistant body some change which has placed it in a condition comparable to that responsible for natural immunity—a condition which merely renders the body a less favorable medium for parasitism by the tubercle bacillus. It is obviously of great importance to continue the attempt to determine what it is that inhibits parasitism in natural as well as in acquired immunity in all infections in which specific bactericidal properties of phagocytes or body fluids cannot be demonstrated.

I wish to emphasize that, in drawing into question the value of allergic hypersensitivity in acquired immunity, I am in no sense questioning the value and good service of the inflammation which attends the allergic reaction. This inflammation, however, appears to me to be directed primarily toward the neutralization of the noxious effects which tuberculo-protein exerts on the hypersensitive tissues, rather than to be an efficient bactericidal attack against the intact, living bacillus. It must be remembered that, in point of fact, the allergic reaction is not an evidence of greater resistance of the individual tissue cells to the protein of the bacillus, but of greater susceptibility. In the allergic, immune body, therefore, one is always confronted with what appears, at first sight, to be a paradox: the infected body is more susceptible at the same time that it is more resistant than the normal one. There is actually, however, no contradiction in this. The infected body prevents the growth and causes the death of the bacilli more readily than does the normal one—that is, it is resistant to living bacilli, at the same time, this resistant body is sensitized to the bacterial protein liberated into its tissues by the disintegration of the bacilli, just as it would become sensitized to any foreign protein introduced parenterally—that is, it is hypersusceptible to tuberculo-protein, for it is generally believed that it is not the intact, living tubercle bacillus which initiates the allergic reaction but, rather, the protein liberated by the disintegration of the bacilli. Even Zinsser, who holds the belief that allergic hypersensitivity is of fundamental importance in acquired immunity, because it sets the inflammatory mechanism



on a "hair-trigger," so to speak, has recently written the following "Bacterial allergy is a condition in which the body is sensitized to a bacterial antigen. We believe that this antigen, in its most potent form, results from biological disintegration of the bacteria. The allergic state represents an increased capacity on the part of the tissues to react to this antigen"<sup>17</sup> According to Zinsser's own definition, therefore, the allergic state in tuberculosis represents an increased capacity on the part of the tissues to react, not against living tubercle bacilli but to an antigen which is liberated as a result of the disintegration of the bacilli. This means that when bacilli lodge in the tissues of the immune body, a mechanism responsible for their destruction must be in operation before the allergic inflammation appears.

I repeat that the capacity for developing hypersensitivity to protein must exist for some serviceable end, but it is one thing to believe that the reaction exists for some useful purpose, and quite another thing to believe that it protects the body against the tubercle bacillus. In spite of certain differences, the various forms of protein hypersensitivity are, in all probability, merely different manifestations of one fundamental type of reaction which is brought into play under different conditions. What the basic intent of that fundamental reaction may be is not known. It has been suggested, for example, that it exists for the purpose of preserving the specificity of the protein of the species. However this may be, the disastrous effects of the repeated introduction of foreign protein into the blood stream (as exemplified by anaphylaxis), or into the tissues (as manifested by tuberculin allergy, or the Arthus phenomenon) may very well be accidental results of a highly organized, benign, serviceable mechanism which, under these circumstances, has been forced into action in situations and under conditions quite different from those which surround its intended activity. From such a point of view, a hypersensitive reaction initiated by the liberation of a bacterial protein from disintegrating bacilli has, basically, the same meaning as a hypersensitive reaction resulting from the deliberate forcing of egg-white into sensitized tissues. It is no more difficult for me to regard the allergic hypersusceptibility leading to tissue damage and inflammation in certain bacterial infections as an unfortunate accident, unnecessary for immunity and merely resulting from the parenteral liberation of foreign protein by the bacteria than it is to regard the anaphylactic state as of no special use in immunity to bacteria, and certainly, an animal may be highly anaphylactic to tuberculo-protein without possessing the slightest degree of acquired immunity to the tubercle bacillus, conversely a superb degree of acquired immunity to the tubercle bacillus may be present in animals which are not anaphylactic at all. Those who feel, on general principles

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17 Zinsser Bull New York Acad Med 4 351, 1928

that since allergy appears during infection it must be of use in immunity, should remember that this other closely related hypersensitive state, anaphylaxis, may also be developed in tuberculosis although it is entirely unessential to immunity

It is obvious that, if allergic hypersensitiveness is not necessary for immunity, procedures aimed at desensitization might be of great value, for desensitization would free the tissues from their disastrous tendency to necrosis, while leaving immunity intact. As a matter of fact, whatever beneficial effects attend tuberculin therapy can, to my mind, be best accounted for on the basis of the resulting depression of allergy, with the consequent greater opportunity for repair to proceed about foci of bacilli, unhampered by allergic destruction of the newly forming granulation tissue. It is interesting that Hamman and Wolman, in their book on tuberculin therapy,<sup>18</sup> make the following statement in their discussion of the patients who improve under repeated doses of tuberculin. "In the majority of cases," they write, "such a change for the better is associated with the development of a tolerance for tuberculin. This is a clinical fact, whatever our theories may be. We must not blind ourselves to the well attested clinical observation that the average tuberculin patient shows, simultaneously with his improvement under tuberculin, a tolerance for tuberculin by whatever route. This remains a fact generally true, in spite of the citations of individual cases showing departures from this rule and in spite of oscillations of theories of immunity." I know that it is ordinarily assumed, not that depression of allergy has favored repair by removing an agency which tends to destroy connective tissue as rapidly as it is formed, but rather that the treatment stimulates the formation of connective tissue, and that allergy becomes depressed because the lesion becomes encapsulated. This I find difficult to believe, for aside from the fact that the method employed in successful tuberculin treatment is exactly the one best adapted for purposes of desensitization to foreign protein in general, it is difficult to believe that the encapsulation of a large tuberculous focus could so markedly reduce hypersensitiveness, while most normal adults carrying about small encapsulated foci retain it in a greater degree. Furthermore, allergy may by desensitization be reduced practically to zero in the human being and in the experimental animal in the presence of lesions which are progressive and by no means encapsulated.

If acquired resistance—the unknown mechanism which restrains the growth of the bacillus in the infected body—is actually (as I believe it probably is in tuberculosis) a thing separate from allergic hypersensitiveness and can be left intact after desensitization has restored the tissues to

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<sup>18</sup> Hamman and Wolman. *Tuberculin in Diagnosis and Treatment*, New York, D. Appleton & Co., 1912.

their normal indifference to tuberculo-protein, the security against necrosis which desensitization assures the tissues would certainly be of the greatest importance. Perhaps in some infections allergy does assist immunity by bringing bactericidal fluids and cells to the spot, but it is important, it seems to me, to do more than merely assume this as a generalization. It is important to study each infection with the purpose of determining, first, whether allergy is essential for immunity to the particular micro-organism under consideration, second, whether the allergic inflammation is actually an efficient bactericidal or growth-restraining agent as regards that particular micro-organism, third, to what degree the hypersensitivity acquired during that particular infection tends to kill tissue, for it is highly probable that this tendency will be found to be different in different infections, and, finally, from a weighing of the information acquired, to decide whether or not procedures aimed at desensitization should be attempted. In some infections the dissociation of allergy and immunity may be more easily effected than in tuberculosis. Dr. Chesney, Dr. Turner and I have recently obtained conclusive evidence of this in an experimental study of immunity and allergy in syphilis. Certainly, in tuberculosis, it is of great importance to know whether the local sacrifice of tissue (which itself, through allergic inflammation and allergic necrosis and softening is commonly enough a direct aid to the extension and spread of the bacilli) is actually necessary in any way for the protection of the body as a whole.

#### CONCLUSION

In conclusion let me say that I am keenly aware of the great attractiveness of the idea that bacterial allergy operates to destroy the invading microorganism, and perhaps it does not play an accessory rôle in certain infections, although I doubt that it is ever the essential basis of immunity. However, the enthusiastic eagerness with which this idea is so generally seized on in the case of tuberculosis may profitably be tempered by a critical examination of the evidence on which it rests. In this paper, I have been able to present only a few points in the analysis of that evidence, but I have wished to emphasize that in the present state of information in regard to tuberculosis it is wiser not to interchange too glibly the terms "allergy" and "resistance." Nor shall one profit by the use of such current evasive phrase as "allergy is an index of resistance," etc. The question to be met squarely is this: Is or is not tissue hypersensitivity to tuberculo-protein *necessary* for the more efficient destruction and restraint of growth of the tubercle bacillus observed in the body with acquired resistance? I have offered here a few of the numerous reasons for the belief that it may not be necessary, but further experimentation directed toward the solution of the problem is urgently required.

## THE ADRENAL GLANDS<sup>\*</sup>

G N STEWART, M D

CLEVELAND

Since 1915, Dr J M Rogoff has collaborated with me in all the work on the adrenal glands. It has been a joint research, and even when I speak in the first person singular I include him. Further, the investigation, although extending over a long time, was planned as one continuous piece of work on the two glands constituting the adrenal bodies. As it was planned, so it was carried out, with few modifications. The work on the interrenal gland overlapped that on the chromaffin tissue, but when the latter had been proved to possess only slight physiologic significance, or, at any rate, not to be concerned essentially in the preservation of health and life, we decided to spend no further time on the medulla but to concentrate all our efforts on the cortex. Many interesting facts, however, were discovered in regard to the liberation of epinephrine from the medulla, and previously known facts were confirmed and amplified, some of which are herein mentioned.

In this paper, no attempt is made to cover the whole field of the physiology and pathology of the adrenal glands. This is much too extensive even to be sketched in the time at our disposal. The literature is vast and continually growing. Unfortunately, much of the work is, for various reasons, so poor that it is kept alive only through the conscientious efforts of authors to notice everything that has been written. It would be a distinct advantage if many papers, not necessarily the earlier ones alone, could be forgotten. To describe everything in detail, to analyze and to controvert what is wrong would require the writing of a shelf of books. A complete account even of what has been already ascertained, or of what is more or less plausibly conjectured, would fill a good sized volume. All that can be done here is to select what seem the most important and best established results, particularly the more recent ones, to connect them, as far as possible, with each other and,

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perhaps, in certain instances to relate them to properties and functions of other tissues, as a contribution toward a future theory of the functions of the glands

The active substance of the medulla having been discovered and isolated at a time when hardly anything was known about the cortex, it is unfortunate, though natural, that adrenalin or epinephrine should have at once assumed the place of the hormone of the adrenal gland. It has been so designated almost everywhere, not only in textbooks of physiology but, with hardly an exception, in textbooks of medicine and in clinical writings generally, this error has persisted to the present hour. As the adrenal gland is unquestionably important, being, in fact, indispensable to life, it seemed necessary to invest the only known active principle of the gland with important physiologic functions, particularly as the pharmacologic actions of the substance (usually in much larger concentration than can ever exist in the arterial blood) are manifold and most striking. Everywhere, then, the importance of epinephrine was emphasized. It sustained the blood pressure by its vasoconstrictor action. It titillated the heart when it tended to lag and grow weary and kept it to its never ending task. It influenced the tone of all muscular structures innervated by the sympathetic nervous system. It caused the pupils to dilate, the eyeballs to appear more prominent and menacing, and the hair on the tail and back to be erected when animals were stirred by rage or anger. It participated in the physical accompaniments of the emotions aroused by combat. It even caused the blood to clot faster if the combatant was wounded. It was the only one of the internal secretions which seemed to be completely anti-pacifist. No wonder it became popular. No wonder many came to agree with Cybulski, who wrote at the time when indications of what is now called epinephrine or adrenalin were found by him in the adrenal veins. "The nervous system is now dethroned." This absurd dictum and all that it implies became embedded in the physiology of the clinician. If standard textbooks of medicine are consulted today as to the pathology of Addison's disease they still announce that it is the loss of epinephrine that causes the chief symptoms, including, of course, the fall of blood pressure. Usually the cortex is never mentioned. The consequence of all this is that the average reader rises from his study of the works usually available to him deeply impressed with the varied and potent actions of the epinephrine liberated by the medulla, but scarcely conscious that the cortex is anything else than what used to be called a vestigial remnant without physiologic significance. It is probably safe to say that nine tenths of the medical profession are completely ignorant of the physiology of the adrenal bodies, or, what is far worse, have minds so well stored with erroneous information that truth finds them hard to penetrate. Many generally

well informed students, if asked what would happen were the adrenal medulla to cease delivering epinephrine to the blood, would probably answer that a severe fall in the blood pressure would occur, while the emotions of the sufferer, in the presence of the physiologic catastrophe, would have to remain unexpressed.

I am not sanguine enough to suppose that such errors can be eradicated easily, nor is it my business to carry on a crusade against them. It is not important that they should linger on for a while. In time all these matters will be put right. On the present occasion, however, the opportunity offered of restating the salient facts in regard to the supposed functions of the medulla need not be neglected. The chief part of the paper will deal with the newer work on the cortex.

To forestall a possible criticism, or at least to prevent ambiguity, it may be stated at the beginning that I generally use the term adrenal rather than suprarenal even in the cases in which the latter is anatomically correct, as in man. In one of the common laboratory animals, the guinea-pig, the large adrenal bodies lie cephalad to the kidneys rather than beside them, and might be denominated suprarenal rather than adrenal glands, if the mere anatomic relations were to govern the terminology. These relations, however, whatever their occasional interest in surgery and pathology, have no functional significance. It seems better, therefore, to employ one name for the same tissues irrespective of their anatomic relations to the kidneys.

The important experimental data have been obtained on the adrenal glands of animals. If the same word is to be employed to characterize one and the same structure, the use of the term adrenal should be extended to take in the human gland. The opposite rule of using the word "suprarenal" indiscriminately in dogs, cats, rabbits, rats, guinea-pigs, etc., as well as in man, is insisted on by some editors for reasons difficult to fathom. It certainly seems clumsy to speak of the suprarenal glands of a rat or a cat—quite as clumsy as it would seem to speak of the adrenal glands of a man. No harm is done in either case if the self-respect of the necessary, harmless contributor is not outraged in the process of securing uniformity.

More than seventy years have elapsed since Addison published his observations on the "constitutional and local effects of disease of the suprarenal capsules." It shows a penetrating judgment that from a clinical and postmortem study of certain cases of the syndrome now called Addison's disease he should have unveiled a relationship, since abundantly confirmed, between the syndrome and a destructive lesion, especially tuberculous, in the suprarenal glands. His observations, however, are not always easy to understand. For instance, in four of the eleven cases described, the lesion was unilateral. Now destruction of one adrenal gland in animals is harmless. Yet, apparently, the

clinical symptoms were present in these four cases as well as in the remaining seven in which the lesions were bilateral. It may be that Addison was in error in regarding the lesion as unilateral in the four cases mentioned. Microscopic examination might have revealed destructive changes in both capsules. Certain more recent writers, however, have described cases of Addison's disease associated with a unilateral lesion.

At that time it was not recognized that the adrenal body in mammals consists of two glands, the cortex or interrenal gland and the medulla or chromaffin tissue. Even to this day it is not uncommon for authors to refer to the adrenal gland as if it were homogeneous in structure and in function. No apology, therefore, need be made for stating at this point that the cortex and medulla are considered herein as two distinct organs. The mere fact that the medulla is embedded in the cortex changes nothing except that it entails some modification of the blood supply. Until this was made clear, it was impossible to advance far in the study of the adrenal glands, just as it was impossible to advance far in the study of the thyroid gland until the parathyroid glands were discovered and shown to be separate organs with completely different functions.

Several years ago, in discussing the subject of adrenalectomy and the relation of the adrenals to metabolism, I stated that "if the cortex is the important part of the adrenal it would seem logical in considering the special relations of the gland to metabolism to take the cortex first. It happens, however, that by far the greatest amount of work has been done upon the medulla, the reason being that it forms and gives off a well characterized substance, epinephrine, which in sufficient doses causes many striking reactions, including definite metabolic effects." For that reason the medulla was taken up first and at considerable length, while the more important cortex was relegated to the end of the paper and treated briefly. In the interval which has elapsed, much progress has been made in knowledge of the cortex, largely through the researches carried out in this laboratory by Dr J. M. Rogoff and myself. Dr de Neckel, Dr R. Dominguez and Dr Ecker have also collaborated with Dr Rogoff in investigating certain points. It will, therefore, be best to reverse the order in the present paper and to deal first with the really important gland of the adrenal body, the interrenal gland or cortex.

#### THE INTERRENAL GLAND OR CORTEX

It is not possible to extirpate the cortex except by removing the entire adrenal body. Proof will be given that the medulla or chromaffin tissue can be taken away without affecting the health or life of the

animal The consequences which follow total adrenalectomy are quite different and may, therefore, be attributed to loss of the function of the cortex

A large proportion of white rats survive indefinitely the loss of both adrenal glands The same is true of wild (sewer) rats, as shown by Bonnet more than thirty years ago Rogoff and de Necker found that in large batches of good stock fully 50 per cent of white rats, and in some batches still more, may survive, apparently for an indefinite time Of adult rabbits, not less than 25 per cent—under the best conditions, considerably more—recover completely after excision of the two adrenal glands and live indefinitely A large additional number survive for several weeks The fact that many rats and rabbits survive the loss of the adrenal glands has generally been attributed to the presence of accessory adrenal glands composed of tissue like the cortex so that in these animals the operation sometimes remains incomplete While this explanation may be accepted for some of the animals it cannot be considered as proved for all Nor has the amount of tissue necessary to keep an animal alive been ascertained so exactly that an accessory, when found can be confidently said to suffice

The dog is an animal in which, according to macroscopic observations, accessory adrenal glands are exceedingly rare One was encountered in 150 dogs, and this was seen at the time of operation and removed Dogs always die after total adrenalectomy If the technic is adequate, they do not die from the operation as such but from the syndrome which is called adrenal insufficiency, and which develops after a longer or shorter period of good health We have accumulated no less than 200 of these "control" dogs in which the adrenal glands were removed one at a time, with an interval of from one to many weeks between the two operations The results on the control animals, not subjected to any treatment, form the indispensable standard of comparison when a given method of treatment, or the effect of certain physiologic conditions on the consequences of total adrenalectomy is being tested In certain cases, the control series has been swelled by the addition of animals in which a given treatment has had a clearly negative result It is not necessary to reproduce tables in which the results on control dogs have been embodied They can be found in several of our published papers

It may be said that most dogs operated on according to our technic survive the removal of the second adrenal gland for at least a week Many live for ten or twelve days, a few for fourteen or fifteen days, and in rare instances the dogs live for fewer than five or six days One dog of 150 was seen to survive sixteen and a quarter days None of the dogs die in as short a time as twenty-four hours, and we are inclined to believe that when an animal survives for only two or three days, it does not die of adrenal insufficiency alone We do not think



averages of such series of much use, but the average for our dogs is about eight days, for the last series it was nine and a half days

Cats survive longer than dogs. The average in our laboratory for nearly fifty cats was eleven days. The majority lived for from one to two weeks. A few survived three weeks, and one about thirty days. One cat survived for thirty-one and a half days, and one, a castrated male, which was not included among the controls, more than thirty-five days. In accumulating control dogs and cats, only male or nonpregnant female animals are chosen. No female ascertained to be in heat at the time that the second operation would be performed is taken. The reasons for these restrictions will appear later.

It scarcely need be said that in all animals used in either series, for control or treatment, most careful search was made both at operation and post mortem for accessory adrenal glands. Accessory adrenal glands were seen in two cats and removed at operation. In one cat, two accessories were observed at the first operation and purposely left behind, a third was found post mortem. The animal lived for fourteen days and was not included among the controls.

Guinea-pigs in our laboratory have been found to survive much longer than any mentioned in the literature, although not as long as cats or dogs. Many of them live about a week—a few longer.

We have dwelt on this matter of the control series because in judging the effect of a given treatment or a given physiologic condition on survival, everything depends on a comparison with a sufficiently large series of controls. In our opinion, these should be operated on by the same observers who operate on the animals in the treatment series and under the same conditions. Only when both series are accumulated in the same laboratory can a real check be made.

Our results differ greatly from most of those in the literature. Beginning with Brown-Sequard, and in the case of other animals than dogs, statements as to the time of survival and the behavior after adrenalectomy are seen to be impossible of acceptance, because the animals obviously died as a result of poor surgical technic rather than adrenal insufficiency. The symptoms of adrenal insufficiency could rarely, if ever, develop clearly and uncomplicated by other symptoms not connected directly with elimination of the cortical functions. Whatever study might be given to the picture, it was bound to be unsatisfactory because of the clouding effects of the operation. Further, the study was necessarily too transitory because the period of survival was so short.

Perhaps the best illustration which can be given of the absolute necessity of good technic in drawing conclusions as to the effects of loss of the adrenal glands is the work of Brown-Sequard. Not long after the publication of Addison's paper, he extirpated the glands in

different species of animals, and is credited with being the first to prove that they are indispensable to life. This conclusion is certainly true in dogs, cats and guinea-pigs, in most rabbits and in some rats, Brown-Séquard, however, did not prove it. All the animals which he operated on, including rats, rabbits, guinea-pigs, cats and dogs died in from nine to thirty-seven hours. Even when he removed only one gland from rabbits, guinea-pigs, cats and dogs, none survived longer than from twenty-three to twenty-four hours. It is now well known that removal of one suprarenal gland, far from being fatal, does not affect the health or shorten the life of any animal operated on under proper conditions. It was pointed out at the time by Phillipeau that there were other causes than the loss of an indispensable function which might account for the fatal consequences of Brown-Séquard's operations, for example, hemorrhage and sepsis, both extremely common. Cooling, perhaps undue prolongation of operations, inadequate care before and after operation and excessive trauma in a field peculiarly susceptible to trauma almost certainly contributed to the bad results. In any case, what has been said shows clearly that Brown-Séquard was not in a position to draw any conclusion from his results.

It has not been sufficiently recognized, perhaps, that the surgical difficulties in adrenalectomy are except in rats, greater than in operations on most of the other endocrine glands. Removal of the thyroid gland is simple, so is removal of the parathyroid glands as soon as they are recognized. Gonadectomy is easy in the male and not difficult in the female in the laboratory animals. Complete pancreatectomy is, of course, an operation requiring skill. Operations on the pituitary gland are difficult on account of the formidable approach and for other reasons. In the case of the adrenal glands, the right gland in the guinea-pig lies close against the vena cava and under the liver; the vessels are delicate and liable to injury. In the rabbit this is true also, but not to the same degree. In the dog, the operative field lies deep and the right gland is close to the vena cava. Next to the guinea-pig, then, among the common laboratory animals, the dog is the animal whose right adrenal gland is most difficult to excise. In the cat, the operation presents no special difficulty on either side. Except for the rat, this is the animal in which the operation is easiest. In all the animals, adrenalectomy is simpler on the left side than on the right.

We believe that not nearly enough attention has been given to the proximity of great numbers of sympathetic fibers and ganglions which are liable to be crushed and torn unless the operator knows the importance of inflicting on them as little injury as possible. The removal of the adrenal glands or of one of them, unless it is done with care, is apt to cause a fall of blood pressure which has nothing to do with the loss of epinephrine previously discharged from the gland, it is,

instead, the expression of a shock-like condition apparently due to the traumatization of these numerous sympathetic fibers. We have often seen this in acute experiments in which the adrenal glands were removed to test the effect on some reaction which was previously obtained. When this shock-like condition supervened, such a reaction as acceleration of the "denervated" heart or vasoconstriction of a denervated limb on stimulation of sensory nerves might disappear, since shock was, of course, unfavorable to eliciting the reflexes. If the blood pressure later recovered with the adrenal glands removed, the reaction might again be obtained. It had not been suppressed because of loss of the epinephrine but on account of the shock caused by the trauma. In view of the fact that no other factor has been responsible for errors in work on the adrenal glands to the same extent as inadequate surgical measures, no apology is required for spending some time on the matter.

#### SYMPTOMS FOLLOWING ADRENALECTOMY

We return to a consideration of the consequences of complete adrenalectomy, which can be studied perhaps most satisfactorily on the dog. A short time is required for a dog to recover from the anesthetic. One of the advantages, probably not a slight one, of extensive experience in performing the operation is that the duration of the anesthesia can be diminished. The ordinary time of the operation with us is from eight to twelve minutes in a dog, and about five minutes in a cat. By that time, the skin is stitched and the anesthetic discontinued. It is, therefore, not to be wondered at that in a half an hour, sometimes less, the dog has generally recovered and is willing to eat, though not permitted to do so. The period of good health is proportional to the total period of survival, so that whether the latter is long or short, about the same number of days elapses between the first development of serious symptoms and death. During the period of good health the animal appears perfectly normal. It preserves habits or tricks which were characteristic before the removal of the second adrenal gland. It is impossible to determine from the animal's behavior whether it has lost its adrenal glands or not. Appetite is unaltered. Dogs that ate voraciously before loss of the adrenal glands eat voraciously after the glands have been excised, those which ate slowly continue to eat slowly. Dogs that liked meat still do so, and dogs previously fond of bread and milk continue to like this ration. The blood shows no changes so far as they have been looked for. The specific gravity, the red cell count, the hemoglobin percentage, the conductivity of the blood and serum, the relative volume of corpuscles as compared with serum, the nonprotein nitrogen, the urea nitrogen, the so-called "undetermined fraction" of the nonprotein nitrogen, the uric acid, the creatinine and the amino-acid nitrogen are not altered, except that in

some cases an increase in the nonprotein nitrogen, urea nitrogen, "undetermined fraction" and relative volume of erythrocytes may be detected a day or so before the first definite refusal of food.

Anorexia is the first and most constant of the serious symptoms which terminate the period of good health. Once declared, it persists, except that occasionally an animal after finally refusing the usual ration may be tempted to eat once, rarely more often, something which it considers a delicacy. Refusal of food is, of course, a common symptom in any sick animal. It cannot be said that there is anything especially characteristic about the anorexia of adrenal insufficiency, except that it is inexorable and that it presages the death of the animal in, at the most, a few days, usually two or three. To an observer who does not know that the adrenal glands have been removed, there is nothing which distinguishes this anorexia from any other anorexia, unless it is an aversion to fat which develops before total anorexia has set in. This point will be considered in connection with the changes in the pancreas, and again in connection with the aversion to fat seen in cases of Addison's disease. The anorexia may be accompanied by emesis. Bile may be present in the vomitus. As a rule the animal does not appear seriously ill at this stage. It is constantly a source of surprise to the observer until he gets accustomed to it, how slight an ailment adrenal insufficiency usually appears to be in a dog, at least until near death. It is the uniform and rapidly fatal result which shows that the symptoms, whether slight or not, are indications of a serious disturbance.

Asthenia, which has been emphasised by some authors as the chief and earliest symptom is not as a rule obvious for some time after the animal has definitely refused food. The error is due to the fact that moribund animals were observed, dying mainly as a result of the operation. Naturally, dying animals are weak. Often the animals are strong on their feet, pugnacious if they were so before, and able to run well if they can be coaxed to try. They are, however, apt to be lethargic, as time goes on, the lethargy deepens into stupor and coma. Convulsions are sometimes seen. On the whole, however, the behavior of the animal after anorexia and the other symptoms have developed often by no means suggests danger to an inexperienced observer. The arterial blood pressure (systolic and diastolic) is not affected by the removal of the adrenal glands, as shown in dogs and rabbits by Rogoff and Dominguez by means of the carotid loop method of van Leeuwen. The pressure was taken at frequent intervals beginning before the removal of the first adrenal gland. Even during the operation, pressure readings were made, as stated, without revealing any change beyond the limits of the ordinary variations. The fall of blood pressure so commonly seen in Addison's disease is, therefore, not reproduced in experimental

adrenal insufficiency, probably because the latter condition is not sufficiently chronic. Undoubtedly, when the animal's circulation has become impaired, as commonly happens when death approaches, there is a fall in blood pressure. It has often been remarked that the pigmentary changes so characteristic of Addison's disease are not found in experimental adrenal insufficiency. One could not expect to find them in animals living only a few hours or days, or, on the other hand, in animals living on indefinitely because of the retention of sufficient interrenal tissue to maintain life. The picture seen in dogs deprived of their adrenal glands is, accordingly, not quite the same as that seen in diseases of human beings. It must be remembered that in Addison's disease the loss of the interrenal tissue is usually gradual as the pathologic process spreads. Sometimes it is apparently due to atrophy or, perhaps to congenital deficiency of the tissue, the glands being represented at necropsy by a few small nodules of the same structure as the cortex.

#### CAUSE OF THE SYMPTOMS AND DEATH

When the question arises as to what causes the symptoms and death in experimental adrenal insufficiency, it must be confessed that at present no definite reply is possible. It must be assumed that an intoxication develops, perhaps creeping on from the first day although not announced for some time by detectable symptoms. The remedial effect of large intravenous injections of salt solutions (Ringer's solution with dextrose) is scarcely to be explained except on the supposition that an intoxication has been produced, through the lack of a substance or substances elaborated by the cortex which prevents such intoxication, or of something which aids in neutralizing the toxic products and rendering them harmless. The increase in the nonprotein and urea nitrogen of the blood and in the "undetermined fraction" of the nonprotein nitrogen, and the diminution in the ratio of plasma to corpuscles, however related to the loss of interrenal function, advance in equal measure with the terminal symptoms. They may, as already mentioned, overlap by a day or so the latter part of the period of good health. The concentration of the blood sometimes becomes extreme, as many as 10,000,000 erythrocytes to the cubic millimeter being present, with the specific gravity of the blood exceeding 1.070. The concentration does not affect the serum, its specific gravity rarely exceeding 1.025 and its protein content being unaltered. The serum calcium usually undergoes an increase at the time of, or sometimes a little before, the development of the serious symptoms, especially anorexia, which terminate the period of good health. The blood sugar remains within the normal limits till near death, when a moderate diminution may occur. The uric acid of the blood undergoes no important change. The creatinine and amino-acid nitrogen sometimes show a small increase. The blood chlorine often undergoes a moderate diminution.

If metabolic or other derangements begin immediately or soon after the removal of the second adrenal gland, they have not yet been discovered. It may be that defensive, neutralizing mechanisms are at work which, for a while, are capable of dealing with the poisons, but ultimately break down. Later on, evidence will be given that the interrenal tissue contains a substance which, when administered to adrenalectomized dogs can lengthen the period of survival beyond anything seen in the control series. If this substance is a hormone normally given off by the gland, it may act by influencing the function of some of the important organs which fail sooner or later in its absence, or it may influence special metabolic processes. Then these organs or processes will be interfered with, and in addition poisons may be produced. Thus, in the case of the internal secretion of the pancreas, insulin supplies something necessary for the normal metabolism of carbohydrates, but in its absence toxic substances are also produced which are responsible for such symptoms as coma. The administration of insulin prevents the development of these poisons by restoring normal metabolism.

In one endocrine organ after another—thyroid and parathyroid glands, pancreas (islets) and interstitial tissue of gonads—active substances have been discovered which substitute for the glands. Even the adrenal medulla, the chromaffin tissue, prepares and discharges into the blood a specific substance, epinephrine which, although of slight physiologic significance, belongs to the group of hormones. Analogy suggests that the adrenal cortex or interrenal gland prepares and liberates a hormone also. To this substance the name interrenalin is given, although it has not yet been isolated.

The question at once occurs. Why do some dogs live much longer than others? No definite answer can be given, but one or two suggestions may be made. It is possible that some dogs have a larger store of the active substance than others, if the substance is stored in other tissues than the interrenal glands. This is on the assumption that it is manufactured solely in the adrenal glands. If so, it may be taken up and stored in other tissues, possibly in the interstitial cells of the gonads or, in the case of the female, in the elements from which the corpus luteum is developed. If that is the case, some dogs may store more than others and, therefore, have more at their disposal when the second adrenal gland is taken out. Then these tissues, the origin of which is probably similar to that of the interrenal tissues, may normally elaborate interrenalin, although it may not be liberated in the absence of any need for it. If liberated it would naturally constitute a small contribution compared with that of the adrenal glands. Another possibility is that some dogs may use up any store of the active substance with greater economy than other dogs. Finally, there may be no store whatever, but the resistance of some dogs to the consequences of loss of the adrenal

glands may be greater than that of others, just as the power of resistance to a disease or a poison may vary. None of these suggestions, or others which might be made, have been tested. The fact, however, that a range of from three to five days to fourteen days or more exists in the period of survival of dogs which possess no interrenal tissue invites speculation. Could the meaning of this variation be understood, much light would probably be thrown on the general problem of interrenal function.

#### POSTMORTEM OBSERVATIONS

The postmortem observations on dogs dying of adrenal insufficiency present some points of interest. The most constant change observed is congestion of the pancreas, usually intense and seldom absent. In cats and guinea-pigs, this is also a practically constant feature, although, perhaps from the small size of the organ, the pancreas is not so red. In all these animals, we have compared the postmortem observations with those in normal animals, and the difference is marked. The meaning of the congestion is unknown, but it would suggest some involvement of the organ due to the loss of the interrenal function. It cannot be stated at present how early this congestion is present, it is possible that it is only a terminal event, developing, perhaps, at about the same time as the anorexia or even later. In animals that have been examined microscopically, it appears to involve both acinar tissue and islets. To what extent, if at all, the secretion of pancreatic juice is affected by the changes in the pancreas, it is at present impossible to say. The loss of appetite for fats at a time when lean meat is still picked out and eaten may be connected with an impairment of the fat-digesting power of the pancreatic juice. In cases of well marked hemorrhagic congestion, the condition of the mucosa of the intestine would itself interfere with the digestion and absorption not only of fats but of other foods. Another striking appearance, although not so constant, is hemorrhagic congestion of the mucosa often associated with the presence of blood in the lumen of the gastro-intestinal tract. Sometimes intense congestion, with hemorrhage into the mucosa and blood in the lumen, is seen throughout the whole gastro-intestinal tract from the cardiac end of the stomach to the anus, but often only a portion or scattered areas of the tract are affected. Bile is nearly always found in the stomach. The esophagus never exhibits any congestion. It is occasionally present in the vermiform process and often in the cecum. In exceptional cases, there is neither congestion of the mucosa nor blood in the lumen. It is probable that the gastro-intestinal congestion is a rather late event, but there is no exact information on this point. It may be present, however, some days before death, blood is sometimes passed from the rectum. The significance of these pathologic changes in dogs dying

of adienal insufficiency is unknown, only they are often so extensive and severe as of themselves to constitute a sufficient cause for the fatal result, and, of course, if present early enough, for the onset of the characteristic anorexia. The congestion in the gastro-intestinal tract and in the pancreas is not merely a part of a general passive congestion of the viscera due to failure of the heart, for it may be extremely marked when the spleen, kidneys and other organs are only moderately or not at all congested. We do not desire to emphasize unduly the gastro-intestinal appearances, for it is known that in other conditions somewhat similar appearances may occur. In cats dying after adienectomy these changes, although often seen, are not usually so intense.

We have suggested the possibility that the gastro-intestinal mucosa may share in the elimination of the poison or poisons developed in adrenal insufficiency and may itself be finally crippled by the poison. An alternative hypothesis is that the cortex produces a hormone necessary, among other actions, for the continued normal functioning of the mucosa and also of the pancreas. In the dog, the appearances suggest that a disturbance of function centering around the alimentary canal is one of the consequences of adrenal insufficiency. That there should be no hemorrhage or hemorrhagic congestion in some of the dogs is, of course, no proof that the gastro-intestinal tract continues to function normally. The persistent anorexia and not uncommon emesis may be primarily due to gastro-intestinal changes not necessarily evidenced by congestion. The gastro-intestinal mucosa may be just as much a point of attack in the cat and guinea-pig, and in those dogs which do not show the appearances in question, as when the striking hemorrhagic changes are present. It is not worth while discussing at present whether the smaller dimensions of the structures, possibly even differences in the quantity or quality of the residues of food in the gastro-intestinal tract, may have a bearing on the matter.

#### THE CAUSES OF THE BREAKDOWN

It has been said that during the period of good health the adrenalectomized dog seems normal in every respect. Nothing suggests that the condition of the animal is serious and, indeed, hopeless. Is this appearance of perfect health fallacious? Are changes already in train which will soon issue in unmistakable symptoms? These questions cannot be avoided, but neither can they be answered at present. As already stated, search has been made by us for changes in the blood which might indicate that something was amiss, perhaps soon after removal of the second adrenal gland, although no visible symptoms had yet developed. Hitherto, all the results have been negative. Only when the train of symptoms appears which indicates that the period of good health is over do recognizable changes in the blood develop, these usually



increase until death. It is clear enough, however, that none of the changes in the blood studied by us follow soon after the loss of the interrenal function. If a poison begins to accumulate from the outset, although causing no symptoms until it has reached a certain concentration, requiring maybe a week or more, its detection is not likely to be easy. All we can say at present, therefore, is that during the period of good health the animal runs along on whatever reserves of interrenalin it possesses, if it possesses such reserves till in a week, more or less, the derangement of function leads to symptoms. If poisonous substances, produced in the absence of the interrenal tissue, are being eliminated or neutralized, it is possible that the period of good health is terminated by the breakdown of the organs concerned, perhaps owing to the harmful effects of the poisons on their own cells. At one time, it was suggested by certain writers including the author that the kidney might possibly be such an organ.

While no exact study of the kidney has been made, such observations as we have accumulated do not indicate that in the dog the kidney is specially concerned. The occasional pathologic changes seen in one or both kidneys are probably no greater than would occur in any large series of normal dogs. In rabbits, interference with a kidney at operation may account for some of the cases of renal change. We are far from regarding the pathologic appearances in the dogs' gastro-intestinal tract as proof that the mucosa takes a leading part in the elimination or neutralization of poisons produced in the body in the absence of the interrenal tissue. Nevertheless, it is well known that the mucosa can take an important place as an excretory organ under certain conditions, for example, when saline solutions are injected into a vein. It was shown by Sheerrington long ago that much of the salt solution passed rapidly into the lumen of the intestine and was then gradually reabsorbed into the blood and eliminated by the kidneys. We have seen the same thing in experiments in which Ringer's solution was administered intravenously to adrenalectomized dogs. These experiments were undertaken to test the value of such injections as a therapeutic measure in adrenal insufficiency.

#### METHODS OF TREATMENT

As soon as we had accumulated a sufficiently large series of control dogs, it became possible to test methods of treatment. The only test which at present can be considered unequivocally positive is a prolongation of life decidedly beyond the maximal time seen in the control series. This is a severe test, as it involves the placing of the animal in such a position, through the treatment, that it can successfully meet not only one but all the emergencies which threaten its life. When positive the test is for this very reason not open to doubt. It

would be much simpler to test the effect of a treatment on a characteristic symptom or on the concentration of a blood constituent, but we are not yet in a position to rely on such tests. Effects such as amelioration of symptoms also have positive value, even when temporary. Let it be repeated, however, that in drawing conclusions as to the efficacy of a treatment we have up to the present refused to accept as a positive result anything short of a decided prolongation of the maximal period of survival, and this in a large proportion of the cases. Some weight can also be given to the fact that a relatively large number of long periods of survival occurs in the treated series, though not necessarily beyond the maximum of the control series. Averages are of little use because of the large variations in the period of survival. They are quite misleading, of course, when they are derived from results obtained in only a small number of animals. A positive result of a given treatment must not be inferred from an apparent increase in the average time of survival unless the first test is positive, that is, unless a considerable number of the animals have lived well beyond the longest period of survival of the control animals.

*Injectiōns of Salt Solution*—As stated, injections of salt solution were one method of treatment studied. This was used for several reasons. If an intoxication develops at the time that the serious symptoms appear or is, perhaps, developing from the time of removal of the second adrenal gland, an irrigation of the poisoned tissues, including the blood, which would wash out the whole or a portion of the poison, is possible. A positive result would be that much evidence in favor of the existence of an intoxication, in addition, it would indicate that the poison, or an important fraction of it, was not yet firmly fixed. A salt solution was purposely chosen because its action would be understood to some extent and would be less complex than that of extracts of the glands. There could obviously be no substitution for the missing interrenal gland, nothing in the nature of a hormone could be supplied. Some dextrose was added, but it is not certain that this was of any importance. The intravenous injection of a salt solution is a feasible therapeutic measure, it was thought that if a certain amount of success was obtained in dogs it might well be considered, that in certain cases of Addison's disease, when the condition suggested intoxication and was in any case desperate, an occasional injection of Ringer's solution (in smaller proportional amount than for dogs) might not be justifiable and even promising. It was found that severe symptoms, such as coma and convulsions, could be temporarily ameliorated, and that in some cases animals might be rescued when moribund, and survive much beyond the maximal period of the control series. Further, it was shown that with daily injections of about 100 cc of Ringer's solution per kilogram of body weight with some dextrose added, many dogs continued in good

health far longer than the maximal period among the control animals. The longest period of survival of dogs treated with Ringer's solution was  $53\frac{2}{3}$  days, nearly four times as long as the maximum period among the untreated control animals, and not much less than the average gestation period of dogs. Other survival periods among the seventeen treated dogs were 38,  $33\frac{1}{4}$ ,  $32\frac{2}{3}$ , 20 (two dogs),  $19\frac{1}{3}$ , 19 and  $17\frac{1}{4}$  days. Nine dogs (more than half of the total number) lived beyond the maximal period of the controls, and four additional dogs almost as long as the maximal period.

Nothing like these results was seen among the much larger number of controls. The results of the injections, therefore, were extremely good. It may be pointed out again that there are necessarily great difficulties to be overcome in adding perhaps forty days to the life of an adrenalectomized dog, which without the treatment would usually live only from six to ten days. It is not too much to say that the animal, although running along week after week as if the suprarenal glands were superfluous, is in reality in constant, and, after the ordinary survival period has passed, in imminent, danger of death. Nothing keeps it alive and, to all appearance, in normal health, except the daily liter, or whatever it may be, of a simple solution of salts, such as Ringer's solution. It is not even ascertained that the injection must be a daily one. Possibly less frequent injections would be better. The dose might also have been too large. It was impossible, even though a great deal of time was consumed in the investigation, to compare different doses, different salt solutions, different intervals between successive injections and different periods after the removal of the second adrenal gland for commencing the injections. There is no reason to suppose that we accidentally hit on optimal conditions. Our results are not the best which can be obtained. The unequivocally positive result of the test for lengthening the period of survival is sufficient proof of the beneficial effect of the treatment when carried on for long periods. Even more impressive although not susceptible of the same arithmetical comparison, is the immediate, almost startling, improvement often produced in animals the condition of which seems desperate, for example, in coma. This improvement may not last long in some cases, but in others the dog may take on a new lease of life. Obviously, the result must depend on the extent of deterioration. In one dog, for instance, convulsions and deep coma developed on the third day after the second operation. It was not expected to live through the night. It recovered, however, under treatment with salt solution, regained health and appetite and died on the thirty-fourth day. Symptoms such as anorexia, therefore, may sometimes be benefited, the animal picking up and beginning to eat again. But when the anorexia is absolute and has lasted for some time this effect is probably rare.

The reason for starting the injections on the day after the second adrenalectomy, that is, long before symptoms of adrenal insufficiency had appeared, was theoretical, although not entirely so. It was thought that, if the injections washed out the poisons, the sooner they were started the better, so as to prevent the toxic substances, as far as possible, from anchoring themselves in vital tissues. Whether that idea is correct or not, it would seem reasonable to suppose that the injections, if beneficial, cannot be begun too early. The postoperative condition of the animal must, of course, be considered. As already stated, our animals recovered from the operation in a short time and were considered fit for injection on the following day. It must be said, however, that a few dogs may not stand so large an injection so soon after a serious operation. It is possible to produce serious effects in such animals, perhaps through dilatation of the heart. The heart's action and pulse should, therefore, be watched while the injection is proceeding. In a typical observation, the dog shows symptoms of increased activity of the bowel during or after an injection, and micturates copiously. If there is no micturition for several hours, suspicion should be aroused.

*Administration of Cortical Extracts*—More directly concerned with the cause of death after loss of the adrenal glands and centering around the question of the existence in the cortex of an active substance capable of substituting for it like hormones of other endocrine glands, are our studies on cortical extracts, which have been going on for several years. As a method of treatment in adrenal insufficiency the administration of cortical extracts is, in some respects, the exact opposite of the injection of salt solutions. Yet the results on the lengthening of the period of survival are not very different.

From several of the endocrine organs, specific active substances have been obtained. In some cases it has been proved, in others it is assumed, that the formation of these substances and their liberation into the blood (or lymph) constitute the function of the gland. Assuredly the proof of the existence of these substances, in some instances followed by their isolation and their synthesis (epinephrine and thyroxin) and the determination of their constitution, has not been an easy task. But starting with the work of Baumann, Oswald and others on the active substance of the thyroid gland, followed by the demonstration, by Oliver and Schafer, that a vasoconstrictor substance can be extracted from the adrenal medulla (chromaffin tissue), it has gradually been shown that active principles can be obtained also from the pancreas (islets), from the parathyroid gland and from the sex glands. These have been proved capable of "substituting" for the glands which contain them, in the case of the thyroid gland and the islets of Langerhans, so that in their absence, or when there is undue reduction in amount or in func-

tional capacity, the artificial administration of thyroxin or insulin, respectively, replaces the deficient internal secretion. Important, even indispensable functions are clearly performed by these substances. The specific substance, parathyrin, formed by the parathyroid glands, the loss of which causes tetany, has also been obtained in extracts by Collip. The increase in the serum calcium (hypercalcemia) caused by its administration throws light on the previous discovery of McCallum that calcium salts prevent or cure tetany caused by removal of the parathyroid glands.

It may be mentioned that the largest parathyroid glands that we have ever seen were those of the adrenalectomized dog which lived longest (seventy-eight days) in the series of animals treated with extracts. We do not venture to suggest that the hypercalcemia often seen in these dogs, although only in the terminal stage or slightly preceding it, is brought about through the parathyroid glands. The relations of the adrenal glands, both interrenal and chromaffin tissue, but especially the latter, with other endocrine glands have often been assumed. Proof, however, is still lacking, save in one instance—the correlation of the interrenal gland and certain cells of the gonads (interstitial cells and the corpus luteum?). Since these tissues appear to be derived from the same embryonic structure, the correlation is easy to understand. Changes in the cortex following gonadectomy, and in the gonads following adrenalectomy suggest also the possibility of a functional connection. The best illustration of this is the influence of "heat" (and pregnancy) on the length of life in dogs after loss of the adrenal glands.

Hormones from the ovary and placenta have been described. One, at least, was partially isolated. Replacement effects have been demonstrated in ovariectomized animals, including congestion, swelling and other external signs of estrus (Doisy and other observers).

The adrenal medulla and the posterior lobe of the pituitary gland yield characteristic substances. While of great pharmacologic and therapeutic importance, it is unknown whether they have physiologic importance. It is not even ascertained whether solution of pituitary gives off the active substance to the blood. The question of the function of the epinephrine produced by the chromaffin tissue of the adrenal body will be discussed later in this paper. More or less specific actions, particularly in relation to growth, have been attributed by some observers to extracts prepared from the anterior lobe of the pituitary gland. As investigation proceeded, and as each gap was filled in, there was an increasing probability that the adrenal cortex would in time be added to the list. The discovery was retarded by the experimental difficulties.

No symptom or blood change was known to us which characterized the condition of adrenal insufficiency. We were unable to determine,

as for instance in the case of insulin, by a simple estimation of a blood constituent, the potency of any extract in counteracting the loss of function of the cortex. If this becomes possible, extracts can be tested much more simply than by determining how long animals survive when they are administered. The labor of bringing our experiments to the present point has been great. The work was planned and begun a good many years ago.

The investigations have culminated in the demonstration, for the first time, that cortical extracts can be prepared which can substitute for the adrenal glands. It was indispensable to prove this in order that further attempts to extract and purify the active substance or substances should be placed on a secure basis. The proof that we obtained such extracts is that among the dogs given intravenous injections of certain extracts (generally on alternate days), a considerable number lived far longer than the maximal period seen in untreated control animals. The volume of the injection was usually 1 cc., so that there could have been no irritation similar to that assumed to result from an injection of Ringer's solution. We are left with the explanation that the extracts supplied something normally supplied by the interrenal tissue. For this we have suggested the name *interrenalin*.

As in the case of the salt solutions, it is not to be supposed that we attained optimal results with the extracts. Larger and more frequent doses might have been better, but this has not been ascertained. The important point is that we did find extracts and did administer them in doses which were clearly efficacious. The extracts were made from the adrenal glands of dogs or from the cortex of animals from a slaughter house. Probably each batch differed from the rest in the concentration of active substance obtained by extraction. We had no means of standardizing the extracts. Different dogs might have responded differently to similar doses of active substance, some requiring larger doses than others to stave off the fatal breakdown. The possession of a large series of control animals, however, prepared by an adequate technique, enabled us to conclude with certainty that the indispensable test, the lengthening of the period of survival, was strongly positive. The period of good health was correspondingly lengthened. Among the dogs which did not actually live longer than the maximal period for the controls a larger number, apparently more proportionally than in the control series, attained the longer periods of survival. Occasionally an animal already beginning to go downhill seemed to be revived by a dose of extract, not immediately as in the case of the treatment with Ringer's solution but after some time. The serious symptoms, when they developed eventually in animals treated with extracts, often seemed to be milder than in the controls. The pathologic appearances seen post mortem were also thought to be less pronounced in many

cases Let it be repeated, however, that at present we do not rely on these subsidiary tests Our positive conclusion is based on the decided increase in the period of survival beyond the maximal recorded for the control animals Since the treated animals differed from the untreated controls only in having received extracts, the lengthened survival must have been due to an action exerted by the extracts, which, it is to be supposed, supplied the material (interrenalin) naturally supplied by the cortex

#### INFLUENCE OF "HEAT" AND PREGNANCY ON SURVIVAL

The interesting observation has been made by us that dogs in "heat" survive the loss of the adrenal glands much longer than the maximal survival period of the controls All the dogs from which the second adrenal gland was removed during proestrus or estrus gave this result One lived until the sixty-fifth day The period of good health was correspondingly prolonged The mechanism by which the consequences of total adrenalectomy are staved off must be different both from that of the administration of extracts and from that of the injection of salt solutions The most plausible view is that changes in the ovary are concerned The similarity in structure, and in the nature of the inclusions, between the corpus luteum and the adrenal cortex has often been pointed out

The inclusions in the ovarian interstitial cells also resemble those of the cortical cells In heat, the changes in the ovary, including the development of the corpus luteum, may render available, in sufficient amount to make up for the loss of the adrenal glands, the indispensable substance produced by the interrenal tissue As the development associated with heat subsides, this supply must fail and the fatal consequences of adrenal insufficiency then develop Of course, it is theoretically possible that the ovarian tissues act by destroying poisons produced in the absence of the adrenal glands Actions of detoxication have been attributed to every endocrine gland until in one case after another a specific substance has been discovered which is necessary to the proper carrying on of particular functions When that has been done detoxication ceases to be mentioned It must not be forgotten, however, that when a metabolic process is no longer carried out in the normal manner in the absence of the necessary hormone, the abnormal or incomplete chemical reactions may give rise to the production and accumulation of substances which act as poisons

Pregnancy, in dogs, is another condition in which we have observed longer periods of survival after adrenalectomy than in the control animals Naturally in a condition associated in itself with formidable risks, not every animal shows a prolongation of the period of survival Indeed, not a few succumb earlier than they would have, had they not

been pregnant. Yet it has been clearly demonstrated that many survive from 20 to 30 days, and some from 30 to 40 days. As long a period of survival as 58 days has been seen. One bitch lived for  $57\frac{1}{2}$  days. One of the pregnant animals survived for 46 days, one for  $32\frac{2}{3}$  days, one nearly 27 days and one more than 25 days. Since every pregnant bitch has necessarily been in heat, it cannot be said offhand to what extent pregnancy contributes to lengthening the period of survival. To settle this statistically would require a great deal of work. Heat causes a slight disturbance compared with pregnancy, and no risk. If the aforementioned view of the nature of the protective influence of heat is correct, it is to be assumed that the changes in the sex glands, proceeding further in pregnancy, are still more efficacious than in heat. The metabolic changes in pregnancy are also greater. If lactation has anything to do with the matter its effect will be added to the other effects of pregnancy. The adrenal glands of the embryo in utero do not appear to be concerned. They are certainly not indispensable, since heat is associated with a marked prolongation of the period of survival. Also, survival much beyond the maximal period in the control animals, has been seen in the pregnant bitch after delivery. In heat and pregnancy it is possible that changes in the uterus may influence the duration of life after total adrenalectomy.

Before leaving the subject of the action of heat and pregnancy, it should be remarked that the discussion is by no means academic. The proestrus or period of the blood-containing discharge in dogs is currently assumed to correspond to menstruation in women. The question will sometimes be asked by patients with Addison's disease, whether menstruation is unfavorable or not in this condition, in any case, it may have to be considered by the physician. Apart from the fact that menstruation may be disagreeable and depressing, especially in the early stages, some patients state that their general condition is distinctly better during menstruation. The question whether pregnancy should be avoided may not arise often, owing to the general condition of the patient. It may sometimes arise, however, or the patient may be pregnant, then there may be the question whether interference should be considered or would be profitable. It would be absurd to claim that our observations on dogs supply data sufficient to settle such questions. But such data as they do supply might be helpful in some measure.

It might be anticipated that in some cases a pregnant animal might react less favorably than a nonpregnant animal to removal of the second adrenal gland. Pregnancy itself being a handicap in certain respects, the surgical operation of adrenalectomy, or possibly the state of adrenal insufficiency may exert an unfavorable influence, so that the period of survival is shortened instead of lengthened. We have seen such instances in dogs. Occasionally, premature delivery may be caused by the operation, although this does not necessarily prevent survival for a longer period than the maximum seen in control animals. In one



dog, labor began half an hour after the operation and the animal survived for twenty-six days, nursing the pups normally. It has not been possible to demonstrate clearly any protective influence of pregnancy toward adrenal insufficiency in cats. Premature delivery is often the result of the operation, which apparently is borne worse by pregnant cats than by pregnant dogs.

It is unlikely that there is an essential difference between dogs and cats in regard to a potential protective influence of pregnancy, although it may be more difficult to demonstrate such an influence in the cat. More attention to the stage of pregnancy at which the second adrenalectomy is made might reveal a period when complications are least likely to occur, a positive effect might then be obtained.

#### DETOXICATING FUNCTION OF THE ADRENAL GLANDS

An assumed detoxicating function of the adrenal glands has been mentioned already. Those who have supported the idea of such a function have usually conceived of the detoxication as applying to many poisons, both bacterial toxins and drugs. Some have held that the cortex is the tissue concerned in this process, the majority of the authors, however, have considered it a function of the medulla. The evidence brought forward in support of the detoxicating function of the adrenal gland has generally been a supposed increase in the susceptibility of adrenalectomized animals to certain toxins or poisons. As in the case of nearly all other studies made on such animals, investigators have often been misled by their failure to appreciate the influence of unskilled surgical procedures on their results. Tests have been made frequently by introducing highly toxic material or depressing alkaloids into moribund adrenalectomized animals thus hastening death when it is already inevitable.

Claims have been made by a number of authors that animals deprived of their adrenal glands are much more susceptible to the poisonous effects of tetanus toxin and of morphine. A review of the literature may be found in papers from this laboratory by Rogoff and Ecker, and Rogoff and de Necker, who investigated the supposed increase in the susceptibility of adrenalectomized rats to tetanus toxin and to morphine. They found no evidence, in a large series of animals, of increased toxicity of these substances after removal of the adrenal glands. Many rats which had been operated on were able to tolerate practically the same doses of the poisons as were tolerated by control animals which had not been operated on. Fully three fourths of the deaths that result from double adrenalectomy in rats occur within a period of ten days beginning on about the fifth or sixth day after the operation. The administration of any poison during or preceding this period, as reported

by other observers, would obviously lead to the erroneous impression that the substance was more fatal than in control animals. Indeed, a harmless substance introduced during this period could be considered toxic if no consideration were given to the fact that the animal was moribund. When, however, these poisons were administered to rats adrenalectomized during the period of good health (that is, before or after the period mentioned), it was found that doses up to the minimal lethal dose for control animals were tolerated by many adrenalectomized rats. Rogoff and Ecker investigated the complementing activity of the blood serum in rabbits on which adrenalectomy had been performed and found no difference from control animals which had not been operated on.

That toxins, diphtheria toxin, for example, may poison the adrenal glands as they poison other tissues, is, of course, true. Some of them may even show a preference for the interrenal or the chromaffin tissue. A not uncommon reaction of the cortex to infections and intoxications is hypertrophy (or hyperplasia). But none of these facts can be taken as evidence of a special detoxicating function. Now that our investigations have proved that an active substance, extracted from the cortex, can greatly prolong life after total adrenalectomy, this substance (interrenalin) takes its place with the hormones produced by the other endocrine glands, and the function of the cortex is to produce it. The theory of detoxication was largely based on the desire to endow this gland with a function. Now that a function has been indicated and one of great importance, for a substance which preserves life cannot be insignificant, it is probable that the theory will retire into the background.

The last speculation on functions of the cortex which will be mentioned is that it is concerned with lipid, especially the production of cholesterol, and governs cholesterol metabolism. There is little or no foundation for this theory. Cholesterol, of course, exists in the cortex in a relatively large amount, along with lecithin. The inclusions of birefringent lipid in the cortical cells, especially in the spongiocytes of the zona fasciculata, are the most prominent microscopic features. They are picked out in polarized light by their property of double refraction. Their impressive appearance does not prove that they play an important rôle. The histologic picture is an uncertain guide as to their function and fate, although some cytologists are convinced that they represent a stage in a process of secretion which culminates in their extrusion into the blood. It cannot be said that any really crucial evidence has been furnished to support this conclusion. We ourselves can only contribute the fact that in our studies on adrenalectomized dogs no definite changes in the cholesterol content of the blood were made out.

## THE ADRENAL MEDULLA

None of the endocrine glands produces an active substance better characterized than epinephrine. Its chemical constitution is understood. It has been prepared synthetically. Its physiologic reactions are numerous and striking. It is known to be found in the cells of the medulla. It is responsible for the brown color which the massive inclusions in the medullary cells assume in chromic acid or chromium salts. It has been proved to be given off to the blood, and it is the only substance of the group in which this has been clearly demonstrated. In numerous experiments on dogs, cats, rabbits and monkeys it has never been missed in the blood of the adrenal veins unless its liberation was purposely interfered with. Its passage from the cells to the blood is strictly under the control of nerves running in the major and minor splanchnic nerves and in branches from the lumbar sympathetic chain. When these are completely cut, no epinephrine is found in the blood of the adrenal veins, although the substance can still be found in the medullary cells. No symptoms are produced by section of the nerves supplying the adrenal gland. A temporary loss of weight may occur but this has no special significance. The animals remain in good health indefinitely. The same is true if the medulla is completely extirpated. It is, therefore, impossible to assign to the medulla any function indispensable to life, or, indeed, any function of physiologic importance. This has seemed disappointing to some authors, they have asked whether it is likely that an organ producing and discharging a substance capable of such striking reactions when administered artificially does not possess physiologic significance. One school of authors apparently accepting the view that under ordinary conditions not enough epinephrine is discharged to cause any definite effect, has put forward the hypothesis that in certain emergencies the output of epinephrine is markedly increased through stimulation of the secretory nerves of the medulla. Certain reactions associated with emotions are supposed to be brought about largely through epinephrine liberated by the adrenal glands. These reactions can be elicited by stimulation of sympathetic nerves and also by epinephrine in sufficient doses. The only question is whether sufficient quantities of epinephrine are liberated per unit of time, under the stress of these emotions, to raise the concentration of that substance in the arterial blood to the level at which stimulation of the structures involved will occur. If such quantities are liberated, it is scarcely necessary to verify the occurrence of the reactions.

We believe that there is no evidence that it makes any difference whether the adrenal glands are discharging epinephrine, are prevented from discharging it, or are absent. The reactions accompanying emotions are the same, quantitatively and qualitatively. We are therefore unable to accept the view that an important, or indeed a perceptible factor, in emotional expression is an increased output of epinephrine.

## CHANGES IN OUTPUT OF EPINEPHRINE

The same considerations apply to the supposed increase in the rate of output of epinephrine caused by stimulation of certain afferent nerves and by general asphyxia. If the rate of liberation of epinephrine is sufficiently increased, any of its physiologic reactions can of course be obtained. In experiments, however, which permitted a quantitative estimation of the epinephrine given off per minute by the intestine segment method, we were unable to find any increase either during stimulation of the central end of the sciatic, the brachial or the splanchnic nerves, or during asphyxia. Stimulation of the peripheral end of the splanchnic nerve caused a large increase, as much as twentyfold, whereas excitations of the central end, interspersed among the stimulations of the peripheral end, had no effect on the rate of output. Numerous reflexes were elicited by the stimulation of the central splanchnic nerve, while it failed to affect the output of epinephrine. We have repeated these experiments on afferent stimulation in several researches, always with the same negative result, and similar results were obtained for asphyxia. Acute cerebral anemia, however, caused by tying off the arteries going to the head, excites an increased output of epinephrine, as was first demonstrated by Rogoff in this laboratory.

It would be inappropriate to use the present occasion for controversial purposes. The only reason for mentioning that our results on certain points differ from those of some other investigators is that the discrepancies involve points of technic, including operative technic, which have been found to influence greatly the consequences of adrenalectomy. Differences in the results of experiments on the survival of animals which always die after removal of the adrenal glands depend essentially on differences of technic, including of course preoperative and postoperative care. The decision must always be in favor of the investigator whose animals live longest, assuming, of course, that adrenalectomy was complete and accessories were absent. There is no reason why discrepancies in the results of acute experiments should not also be due to differences in the operative work. If one observer, for instance, fails to obtain a reaction (for example, acceleration of the denervated heart or shrinking of the denervated limb on stimulation of the sensory nerves) when the adrenal glands are eliminated, while another succeeds in obtaining it, the decision must be in favor of the latter who has been able, by better technic, to eliminate the glands without abolishing the reaction. The best method is to perform the operation, partly or wholly, some time before the experiment, which is made after complete recovery from the operation. In any case, we consider that extreme care must be exercised in removing the adrenal glands. Clipping off the veins tightly enough to prevent passage of blood from the glands is the least harmful procedure for those whose

experience in these operations is not extensive. This does not abolish the reaction of the limb caused by stimulation of the sciatic nerve, although it can be verified that the block on the adrenal veins is complete. The same considerations apply to operations on the adrenal glands in the experiment on the denervated heart. The crucial test is to perform the experiment after proper elimination of the glands. We have obtained the reactions, often in undiminished intensity, in their absence. It is, therefore, impossible for us to believe that it is correct to attribute the reactions solely to the reflex discharge of epinephrine. If the reactions can be typically elicited with the glands lying in a dish, the adrenals are not essential to their production.

The positive observations on the influence of sensory stimulation and of asphyxia reported by certain Japanese observers who used our intestinal segment method, have been thoroughly considered and checked by us. We may report on this matter in another paper. We have no hesitation in stating that their conclusions are based on an imperfect application of the method. Their values for the concentration of epinephrine in the blood of the adrenal veins and, therefore, in the outputs, are loaded with a serious error which makes them much too great, incredibly great to us, in many instances. We believe that this is due to the cumulative effect of more than one mistake in the application of the method. In some cases, acceptance of the nominal concentration of epinephrine in the standard instead of the real concentration may be a factor. Material loss of epinephrine from solutions made up at the beginning of the test and kept standing, with frequent opening and introduction of pipets into the bottles can occur. We make up each specimen of epinephrine just before application to the segment. If an error of this nature is made, the effect will be to increase the apparent concentrations (and outputs), and the observer who obtains the smaller concentrations may be presumed to have avoided error from this cause more successfully than he who obtains the larger concentrations. When one of the Japanese observers finds a concentration of 1:250,000 in the initial sample of blood from a dog, weighing less than 12 Kg, with a flow of blood of 30 cc per minute from the adrenal glands, we can only say that there is a big error somewhere. We have never seen any condition like this in the large number of dogs on which we have made estimations. The output for the animal per minute is 0.12 mg of epinephrine (the observer gives it as 0.012 mg, but this is obviously an error if the concentration is given correctly). If this output were maintained for eight or ten minutes only, an amount of epinephrine equal to the entire store in the glands would be given off. He does not point out this amazing result or make any comment on it, it simply goes down in the table. When another of the Japanese investigators finds in a cat a concentration of 1:40,000 in the blood of the adrenal vein, probably about

1 20,000 in the serum (after nicotine), no suspicion is betrayed that results of this kind tend to discredit the paper. Yet in discussing reports of other authors on perfusion experiments with the adrenals of oxen (a poor method for studying the secretion of epinephrine) a point of exclamation is inserted by the observer when he mentions that concentrations of from 1 100,000 to 1 20,000 (1) were found in the perfusion fluid. The point (of exclamation) is well taken. In a deafferented dog, that is, one in which the posterior roots supplying the operative field have been cut, a concentration of 1 70,000 was found in the initial specimen of blood, with a correspondingly large output. Nothing like this was found in the rest of the experiment, even when sensory nerves were stimulated. The explanation given is simply that the dog was excited and objected to being fastened. No such concentrations and outputs were found in initial specimens from other dogs of the series which behaved in the same manner. There are numerous records of excessive concentrations in practically every table in the series of papers, concentrations such as we have not seen under similar conditions, and many of which could be estimated by a colorimetric method. In our own investigations, it was only when the output was greatly stimulated (by nicotine) that concentrations capable of being estimated colorimetrically were seen, although they were much smaller than those given by the Japanese investigators. On internal evidence, therefore, we must decline to accept the results of these workers, we object as strongly to the figures by which they profess to confirm our work (strychnine, nicotine, etc.) as to the figures on which they rely when they come to conclusions different from ours (sensory stimulation and asphyxia).

Other observers who have obtained what they consider positive results have used methods which did not permit estimation of the rate of output of epinephrine or of changes in that rate (anastomosis of the adrenal vein of one dog with the jugular vein of another, etc.) Their conclusions are based on the occurrence of one reaction or another which they interpret as indicating an increase in the output of epinephrine during sensory excitation or asphyxia. But without exception the supposed demonstrations fail to show that the output is increased. A great defect in these methods is that changes in the rate of blood flow from the adrenal gland and the rate of passage of epinephrine into the reacting animal are not controlled.

#### ACTION OF DRUGS ON THE OUTPUT OF EPINEPHRINE

The action of certain drugs, first investigated by us, on the output of epinephrine has been mentioned incidentally. It deserves fuller treatment for its physiologic interest and, in some instances, because of a possible therapeutic value. Space is not available, however, for

a detailed discussion. It will suffice to say that some drugs increase the rate of output, for example, strychnine. The increase may be to many times the initial value, and the arterial blood may become charged with detectable concentrations. The action of strychnine is central, section of the splanchnic and other nerves going to the adrenal glands prevents it. An increase to 100 times the original (diminished) output in an animal with a high section of the cord has been seen on administering strychnine. Morphine (in cats) and physostigmine are other drugs which increase the output.

Other drugs diminish the output of epinephrine. Nicotine is an example. The paralyzing action is preceded by a brief period (from half a minute to a minute) during which the output is greatly increased. The increase swings over quickly into a marked decrease, which lasts much longer but can end in a recovery if the dose is not too great. The stimulating action can be elicited after the splanchnic nerves, etc., have been cut, it is, therefore, not a central action.

A large number of drugs may be expected to exert an action on the output of epinephrine. We investigated a considerable number and had planned to examine a good many additional drugs likely to be found active, but the work on the cortex came to the point at which all our available time was absorbed. It was necessary to abandon further work on the action of drugs on the output of epinephrine at least for a time. Whether such an increase as can be caused by strychnine and other drugs would ever be useful could only be determined by experience. Calculation, however, of the greatest possible effect of safe doses on the output might indicate whether the corresponding increase in the concentration of epinephrine in the arterial blood would be of any use in certain conditions. It is easy, of course, to introduce artificially far greater amounts of epinephrine than can ever be given off from the glands. Usually the results have been disappointing. That epinephrine should have no substitutive effect in experimental adrenal insufficiency, as shown by us many years ago (for the first time, we believe, on properly prepared animals), and in Addison's disease, is to be expected since the loss of the cortex is the important lesion in these conditions.

#### COMMENT AND SUMMARY

Our first step was to show conclusively that the interrenal tissue (cortex) is the part of the adrenal body indispensable to health and life. The chromaffin tissue (medulla) can be destroyed, the discharge of epinephrine from it arrested by section of its nerve supply, or both operations can be performed without ill effect, immediate or remote, and, indeed, without any noticeable effect.

We then studied the symptomatology and pathology of the condition which follows complete adrenalectomy (total adrenal insufficiency)

and determined the length of the period of survival and the period of good health in a large series of dogs, destined to serve as controls for our studies on the influence of treatment by cortical extracts and in other ways. Nothing in the literature was found to be of value, because it was clear that the animals had died largely in consequence of inadequate operative technic and seldom, if ever, from adrenal insufficiency alone. Our results proved that dogs properly operated on, and under proper conditions, lived in a majority of the cases from 6 or 7 to 8 or 9 days. A good many survived well into the second week, and not a few lived for 13 or 14 days. Occasionally a dog lived a day or two longer. The average for the first 120 dogs was 7 days, and for the later series about 8 or 9 days.

Cats live longer than dogs, the average period of survival in our series being 11 days. Many cats live for 2 weeks, a few 3 weeks. Occasionally an animal survives longer than the fourth week. One lived for  $32\frac{1}{2}$  days.

A series of animals in which treatment is given (for example, with extracts), in order to yield a definitely positive result, must show a fair number of animals surviving well beyond the maximal periods of life in the control series, also, a considerable number should reach the longer periods of survival of the control animals. A comparison of the averages is not at all satisfactory unless the tests mentioned give strongly positive reactions. If a series of treated cats were to show a few animals living from three to five weeks and many of them living from nine to fifteen days, this could not be regarded as a positive result. Similar results for dogs, however, would be considered positive. Since the comparison depends absolutely on the control animals, too much care cannot possibly be taken in accumulating a good control series.

We have shown for the first time that extracts of cortex, from the adrenal glands both of dogs and of animals from the slaughter-house, cause prolongation of life when injected into dogs, far beyond any results seen in the control animals. The period of good health is correspondingly prolonged. The interrenal tissue therefore contains and, it is to be supposed, produces a substance which we suggest may appropriately be termed *interrenalin*, and this substance has the power of staving off death in adrenalectomized dogs. As soon as the difficulty of this feat is realized, the question whether life can be prolonged ten days, fifty days or hundreds of days ceases to take first place. The problem becomes a matter of dosage, the preparation of the extract, etc. If life is prolonged beyond a doubt by the action of an extract, the active substance in some way or other must enable the organism to surmount all the emergencies which threaten its life and will inevitably destroy it when it has reached the span, brief at best, allotted to dogs deprived of the adrenal glands and not subjected to



treatment It is not a small reaction of an unimportant substance which neutralizes the poisons destined to overwhelm the untreated animal within a week or two, or prevents their development by contributing to the metabolism what is necessary to keep it normal, nor is it a small reaction of an unimportant substance which staves off the breakdown, probably centering about the gastro-intestinal tract, and announced first of all among the serious terminal symptoms by the onset of anorexia It is a potent reaction of a highly significant substance that takes hold of a dog destined to die, let us say at the end of the tenth day, and carries him on in good health until the end of the twentieth or thirtieth day, or sometimes much longer The test is, indeed, so severe that it ought not to have occasioned disappointment had the series in which treatment was given rarely revealed an animal living longer than any of the controls There would still have been good reason to believe in the existence of a cortical hormone and the possibility of substitution of it for the missing interrenal tissue Clear and definite proof however, which must be accepted by everyone would not have been obtained It is quite another thing to study a symptom not in itself acutely fatal in order to see whether treatment with extracts has any effect on it This could be done with insulin by estimating the sugar content of the blood, but nothing of the kind is possible, at present, in the case of the active substance of the cortex It is true that we have gained the impression that some of the symptoms, especially the anorexia and what often characterizes it, the aversion to fats, may be modified by treatment But this is too vague to serve as a crucial test Nor does it seem possible at present to employ the development of the increase in the nonprotein nitrogen, the urea nitrogen etc, as a test of the efficacy or inefficacy of a treatment, for the change occurs when the severe terminal symptoms appear or are about to appear, when these symptoms show themselves there is no reason for troubling about less evident changes

It would be premature to attempt to decide at present what the function of "interrenalin" is Pharmacologic studies may throw some light on the question Its influence on the general metabolism or on some special metabolic process must, of course, be investigated The fact that in the untreated animal, as has been mentioned, the breakdown seems to center around the gastro-intestinal tract and that the pathologic changes are prominent there suggests that the cortex has some special relation to that tract including the pancreas In Addison's disease gastro-intestinal symptoms are among the classic features We have seen at autopsy in a case of acute adrenal insufficiency a condition (gastro-intestinal congestion hemorrhage blood in the lumen and congestion of the pancreas) precisely resembling what is so often observed in dogs dying after loss of the adrenal glands The necropsy showed destruction and atrophy of the glands The relationship, however, is not asserted, it is

merely suggested as a hypothesis. It is uncertain whether the asthenia, which develops sooner or later following the appearance of anorexia, is so specific that the cortex must be assumed to bear a special relation to the neuromuscular system.

Whatever the function of the cortex may be, the artificially administered extracts substitute for it, so that the animal, so far as is known, remains entirely normal. It is possible, however, that even from the first day, cumulative changes occur, although they escape detection, which in the long run, culminate in the abrupt appearance of the terminal symptoms and death.

If it is the office of the cortex to contribute to, perhaps to control, the functioning of certain tissues or organs or certain metabolic processes, these will, of course, suffer derangement after removal of the adrenal glands. In addition to the loss of these functions and, of course, connected with it, the development of metabolic faults or faults of intestinal absorption may lead to the accumulation of poisons. In fact, a marked feature in animals dying of adrenal insufficiency is an intoxication, usually revealing itself some time after the anorexia has appeared, deepening as the end approaches, and finally submerging the central nervous system and affecting the circulation. One can think of loss of the cortical active substance, therefore, as influencing the organism in two ways: derangement of the mechanisms or processes which it normally controls, and the development of poisons owing to that derangement. These two factors are not mutually exclusive. An analogy may be found in diabetes. Lack of insulin not only interferes with normal carbohydrate metabolism, leading to an increase in the sugar content of the blood, but also leads to the accumulation of substances associated with the deranged metabolism, which may cause diabetic coma. That an intoxication is present in total adrenal insufficiency is, in any case, certain. The condition can be relieved, as we have shown, by the intravenous injection of salt solutions. These obviously cannot supply a hormone, and may act by washing out injurious substances. Dogs have been kept alive by this treatment for as long as fifty-four days after removal of the second adrenal gland. Many lived far beyond the maximal period seen in the controls. Some were rescued after serious symptoms (for example, coma) had developed, and survived for many days thereafter.

It is shown that no function indispensable to life is performed by the medulla. Indeed after the destruction or denervation of the medulla, or both, everything goes on as before, the animal lives on indefinitely in good health and is indistinguishable in its behavior from an animal which possesses its adrenal chromaffin tissue. One deduction from this fact is that there is no foundation for the view, almost invariably expressed in clinical writings, that Addison's disease is due to loss of

epinephrine Some physiologists, on the strength of ambiguous observations interpreted as indicating a reflexly increased output of epinephrine, have unduly stressed, we think, the importance of the part played by the medulla in vascular reactions and in the reactions associated with the expression of emotions If no change is caused by elimination of the medulla, epinephrine from the medulla does not exercise important functions

A detectable content of epinephrine has always been found by us in the blood of the adrenal vein, although too small for detection in the arterial blood owing to the great dilution The output of epinephrine is much increased by stimulation of the peripheral end of the splanchnic nerves, according to our quantitative confirmation of previous workers It is greatly diminished or abolished by section of the nerves going to the adrenal glands Whether the epinephrine secretory nerves regenerate after section cannot be stated definitely, after many months, the output of epinephrine is still much diminished The concentration of epinephrine in the blood of the adrenal veins is approximately in inverse ratio to the blood flow, so long as the flow is not too small The output is markedly increased by certain drugs, for instance, strychnine, physostigmine and, for a brief time (usually a minute or less), nicotine It is diminished by other drugs, such as nicotine (following the brief increase) It is increased, although not beyond the maximum of the ordinary output (in cats), by acute cerebral anemia

The foregoing observations have been confirmed by subsequent investigators While we have been unable to measure a clear difference in the output of epinephrine during the excitation of sensory nerves or during general asphyxia, some other observers claim to have done so

It may be asked, what then is the function of the medulla? In the past, errors have been made in attempts to provide this gland with a function I should be loath to conclude that it is the "roi faineant" of the endocrine glands, a kind of personage little known to physiology To say that it must be doing something, is a proposition which surely is not worth while contradicting It may even appear self-evident to some The real question would be, is it doing anything worth while, anything that can properly be spoken of as a function? Does it keep up the blood pressure? The blood pressure, however, is not altered, either during or after removal of the glands The point of view is sometimes shifted by the assumption that the extracapsular chromaffin tissue is doing the same thing as the medulla, turning out the necessary epinephrine, and that epinephrine is not lacking after elimination of the adrenal glands Those who believe that reactions, such as those previously mentioned, are abolished when the glands are eliminated, can hardly acquiesce in this conception There is experimental evidence against it When more is known of the formation of epinephrine and

its forerunners, new light may be thrown on the question under discussion. We cannot accept lightly the view that the medulla has no physiologic function, but is important only as raw material for the manufacturing druggists.

There is evidence that in certain forms of experimental hyperglycemia, epinephrine from the adrenal glands may be a factor, although usually a minor one. Thus, puncture at a certain part of the floor of the fourth ventricle causes hyperglycemia and also an increased output of epinephrine. The hyperglycemia is well obtained when the adrenal medulla has been eliminated, and is dependent on splanchnic nerve fibers going to the liver. How much it is aided, if at all, by the increased output of epinephrine, dependent on splanchnic nerve fibers leading to the adrenal glands, depends merely on the rate and duration of the increased output. If the concentration in the arterial blood is increased beyond the threshold value needed to cause epinephrine hyperglycemia and is maintained above this value long enough, a part of the effect will be due to the epinephrine. The hyperglycemia associated with asphyxia does not seem to have an adrenal element. No difference has been found in the amount of the hyperglycemia whether the medulla was eliminated or not. On the other hand, the hyperglycemia caused by morphine (in cats and dogs) is greatly diminished or abolished when the adrenal medulla is eliminated. Such observations suggest, although they do not prove, that epinephrine may exert some influence on carbohydrate metabolism. But it must be remembered that, so far as we know, the concentration of epinephrine in the arterial blood never under physiologic conditions approaches the level at which it would itself cause an increase in blood sugar. There is no evidence that epinephrine from the adrenal glands is the factor which causes hyperglycemia when the function of insulin is interfered with. Hyperglycemia in the depancreatized dog is well marked after elimination of the adrenal medulla.

In considering the question of functions of the medulla it should be kept in mind that no important function can in any case be assigned to an organ the loss of which causes no symptoms. It is not so with the thyroid and the parathyroid glands, the islets and the adrenal cortex, their physiologic value is revealed by the consequences of their removal. They may, therefore, be assumed and are known to exercise important functions. It may seem curious that the adrenal medulla is abundantly supplied with nerves which control the output of epinephrine strictly, while it has not been proved that the production and discharge of the important hormones of the thyroid and parathyroid glands and islets are under the control of nerves. The adrenal cortex functions normally when the gland is denervated. If, as is currently believed, the adrenal medulla is composed of cells representing genetically sympathetic ganglion cells, it is to be expected that it should differ from

the other endocrine glands enumerated for all of them are of quite different origin. The pituitary gland is left out of the discussion, little is known about its functions. Genetically, the anterior lobe would fit in with some of the other endocrine glands but not with the adienal medulla.

We have suggested as a possibility that the reason for the close control of the output of epinephrine by the nervous system may not be to keep up the concentration in the arterial blood to a certain beneficial level, but to keep it below a certain harmful level. In the adrenal glands, there exists a stock of epinephrine which under abnormal conditions (for example, massage) can be liberated, not all at once, but so rapidly that harmful concentrations might be reached. This stock, amounting usually to about one-thousandth of the moist weight of the adienal glands, possibly 1 per cent of the moist weight of the medulla, could easily be dangerous were it possible for it suddenly to escape into the adrenal veins.

It is impossible to go into the interesting observations, first put on a sound basis by Elliott, on the store of epinephrine. This, of course, represents a balance between production and discharge, its amount gives no direct information as to changes in the rate of output. Intense and prolonged emotional disturbance causes no effect on the store of epinephrine, but numerous drugs diminish it greatly.

# THE PATHOGENESIS OF ASPIRATORY ABSCESS OF THE LUNG

ITS POSSIBLE RELATION TO ABSCESS OF THE LUNG  
FOLLOWING TONSILLECTOMY \*

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Pulmonary suppuration following tonsillectomy occurs with sufficient frequency to arrest the attention of both the surgeon and the internist, but the exact method of its development is still in dispute. Aschner,<sup>1</sup> who studied the different types of pulmonary suppurative lesions encountered in the human being in the material obtained from resections of the lobe performed by Lilienthal, differentiated the following types: (1) bronchiectasis, (2) bronchiectatic abscess, (3) suppurative pneumonitis, and (4) extrabronchial abscess. Groups 3 and 4 frequently merge into each other, as areas of suppurative pneumonitis may break down and develop into a large extrabronchial abscess. It is the bronchiectatic abscess group which was of particular interest in the present investigation, as in each of the ten cases studied by Aschner this condition followed the operative removal of the tonsils and adenoids under general anesthesia. In one of the four cases of suppurative pneumonitis, the condition developed a few days after tonsillectomy, in the other three, as a sequence to pneumonia.

The clinical occurrence of postoperative abscess of the lung has been extensively reviewed by Cutler and Hunt<sup>2</sup> and by Schlueter and Weidlein.<sup>3</sup> It is surprising to note the exceedingly large number which has followed tonsillar operations. In a series of 1,908 cases of abscess of the lung reported by the Schlueter and Weidlein, 515, or 29.6 per cent, were postoperative, and of these tonsillectomy contributed 268,

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\* From the Laboratories of the Mount Sinai Hospital.

\* Simultaneously with the submission of this article, a paper containing experimental evidence similar to that herewith reported was published by Minas Joannides (*The Etiology of Pulmonary Abscess, Surg Gynec Obst*, October, 1928, vol. 47).

1 Aschner, P. W. The Pathology of Lung Suppuration, *Ann Surg* **75** 321 (March) 1922.

2 Cutler, E. C., and Hunt, A. M. Post-Operative Pulmonary Complications, *Arch Surg* **1** 114 (July) 1920, Post-Operative Pulmonary Complications, *Arch Int Med* **29** 449 (April) 1922. Cutler, E. C. The Etiology of Post-Operative Pulmonary Complications, *S Clin N Amer* **2** 935 (Aug.) 1922.

3 Schlueter, S. A., and Weidlein, I. F. Post-Operative Lung Abscess, *Arch Surg* **14** 457 (Feb.) 1927.

of 14.6 per cent of the entire group. Of course, this group includes reports by authors who stressed tonsillectomy as the most frequent predisposing factor of postoperative abscess of the lung. On the other hand, Lyman,<sup>4</sup> who recorded 20,000 tonsillectomies performed under nitrous oxide anesthesia in the medical department of Washington University, did not report a single case of postoperative abscess of the lung. Hedblom<sup>5</sup> recorded only 2 of 20,000 at the Mayo Clinic. Moore,<sup>6</sup> publishing data of 450,000 tonsillectomies, obtained through questionnaires, reported abscesses in 202 cases, an average of 1 in every 2,500 to 3,000. Herb,<sup>7</sup> in a series of 12,045 operations on adenoids and tonsils, saw 2 abscesses of the lungs. Glowacki,<sup>8</sup> collecting data from various hospitals in St. Louis, found 1 in every 358 tonsillectomies, and Keiper<sup>9</sup> stated that 1 of 781 tonsillectomies was followed by abscess of the lung.

Obviously, such apparently conflicting statistics give rise to the questions: 1. How many of these cases were followed up after tonsillectomy? 2. What part does individual susceptibility to pulmonary infection play in its occurrence? 3. Is the presence of preoperative respiratory infections of importance? 4. What rôle, if any, does operative technic assume in the pathogenesis?

It is not within the province of this paper to enter into a discussion of all four questions. Some have already been covered by Myerson,<sup>10</sup> Wessler<sup>11</sup> and others. My task is rather to review the clinical observations briefly only as far as they may have a bearing on the pathogenesis of abscess following tonsillectomy, to sift the available data with reference to the two outstanding hypotheses, namely, the

4 Lyman, H. W. Relation of Nose and Throat Operations to Lung Abscess, *J. Missouri M. A.* **20** 418 (Dec.) 1923.

5 Hedblom, C. A. The Surgical Treatment of Acute Pulmonary Abscess, *Illinois M. J.* **47** 267 (April) 1925.

6 Moore, W. F. Pulmonary Abscess. An Analysis of Two Hundred and Two Cases Following Operative Work About the Upper Respiratory Passages, *J. A. M. A.* **78** 1279 (April 29) 1922.

7 Herb, I. C. Post-Operative Lung Complications, *J. A. M. A.* **79** 339 (July 29) 1922.

8 Glowacki, B. F. Pulmonary Abscess. A Study of Ninety Cases, *Laryngoscope* **33** 153 (Feb.) 1923.

9 Keiper, G. F. The Tonsil Question Up to Date, *Laryngoscope* **31** 777 (Oct.) 1921.

10 Myerson, M. C. Pulmonary Aspects of Tonsillectomy Under General Anesthesia, *Laryngoscope* **32** 929 (Dec.) 1922, Lung Abscess Following Tonsillectomy. A Contribution to the Etiology, *Arch. Otolaryng.* **1** 137 (Feb.) 1925.

11 Wessler, H. Lung Abscess and Bronchiectasis. A Clinical and Roentgenological Study of 100 Cases, *Am. J. Roentgenol.* **6** 161 (April) 1919, Suppuration and Gangrene of the Lung. A Study of 100 Cases, *J. A. M. A.* **73** 1918 (Dec. 27) 1919.

embolic and the aspiratory origin of abscesses following tonsillectomy and finally to present experimental evidence which tends to corroborate the aspiratory theory

In considering the pathogenesis of abscess of the lung following tonsillectomy, three methods of infection naturally suggest themselves (1) by direct lymphatic extension from the operative area (2) by way of the bronchi through aspiration and (3) by way of the blood stream in the form of septic emboli

In the assumption of the lymphatic route as a means of transmission, Clendenning<sup>12</sup> laid a great deal of stress on the work of Grober<sup>13</sup> who tried by experimentation on animals to establish a connection between the lymphatics of the neck and those of the lung. The latter drew his conclusions from experiments performed on twenty-eight animals, dogs and rabbits three of which were successful. The injection of coloring matter, such as Chinese ink into the tonsils showed the connective tissue of the neck along the larynx to the aperture of the thorax colored symmetrically. "The lymphatic glands along the large blood vessels, as well as those in the supraclavicular region were deeply stained. The coloring matter was found within the lymphatic vessels and in the paravascular spaces. A fibrous exudate was found in the apexes of both lungs thus forming a bridge of inflammatory material from the parietal to the visceral pleura. The coloring matter was also present in the exudate. The glands of the mediastinum were stained on the left side as were also the bronchial glands. On the basis of these experiments, Grober built the hypothesis "that tuberculous infection of the apex of the lung may take place via the deep lymphatic chain the supraclavicular glands thence to the parietal lymphatic vessels where an inflammatory exudate is thrown across the visceral pleura". The evidence presented however, is insufficiently convincing and is not substantiated by the well known studies of W. S. Miller,<sup>14</sup> whose investigations do not in any way indicate a direct connection between the cervical lymphatics and those of the lung. Nor has Most<sup>15</sup> succeeded in demonstrating any

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12 Clendenning L. The Cause of Abscess of the Lung After Tonsillectomy, *J. A. M. A.* **74** 941 (April 3) 1920, Abscess of Lung, *Laryngoscope* **32** 128 (Feb.) 1922

13 Grober. Ballenger Diseases of the Nose, Throat and Ear, Philadelphia Lea & Febiger, 1914, p. 398

14 Miller, W. S. Some Essential Points in the Anatomy of the Lung. *Am. J. Roentgenol.* **4** 269 (June) 1917, The Vascular Supply of the Pleura Pulmonalis, *Am. J. Anat.* **7** 389, 1908

15 Most, A. Die Topographie des Lymphgefäßapparates des menschlichen Körpers in ihren Beziehungen zur den Infektionswegen der Tuberkulose. *Bibliotheca Medica* part C, no. 21 Stuttgart, Untersuchungen ueber die Lymphbahnen an der oberen Thoraxapertur und am Brustkorb. *Arch. f. Anat. u. Entwicklungsgesch.* **30** 1, 1908



communications between the lymphatics draining the tonsillar region and those draining the lung and mediastinum

From a clinical point of view, the majority of opinion is in favor of the aspiration theory. Schlueter and Weidlein stated that in a census of recent contributions on the subject, forty declared themselves in favor of aspiration as the cause of abscess, while only ten favored embolism. The proponents of the embolic theory of the causation of abscess following tonsillectomy based their conclusions on the following facts: (1) the failure to produce abscess of the lung experimentally in dogs by endobronchial methods, (2) the relatively frequent development after local anesthesia, (3) the late development of symptoms, (4) the high incidence following other operations performed in potentially infected fields, and (5) the greater percentage of occurrence after procedure in mobile areas.

The reasons advanced for the aspiration theory are summarized as follows: (1) the common association with general anesthesia, (2) the clinical evidence that aspiration occurs, (3) the high incidence after tonsillectomy and other operations on the upper respiratory tract, and (4) the frequency of involvement of the lower lobe.<sup>16</sup>

The unsuccessful efforts of workers previous to 1926 to reproduce experimentally by aspiration pulmonary suppuration in dogs, together with the considerations enumerated, induced Cutler,<sup>2</sup> Schlueter,<sup>3</sup> Holman<sup>17</sup> and others to favor embolism rather than aspiration as the most important factor in the causation of postoperative suppuration of the lung. They argued that tonsillectomy is a common operative procedure, and yet the experimental production of abscess of the lung by aspiration is an impossibility. It must be noted, however, that their failure to produce abscesses in dogs by aspiration cannot be held as conclusive evidence that such a mechanism does not occur in human beings, especially in view of the innumerable clinical examples of pulmonary abscesses following the aspiration of foreign bodies. To this, however, I shall refer later.

In support of the embolic theory, these workers further adduced (1) the clinical evidence of some observers who have collected a greater percentage of pulmonary complications in patients operated on under local anesthesia (these pulmonary complications, however, included embolic pneumonitis without suppuration), (2) experimental observations which support the view that so-called postoperative pneumonias

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<sup>16</sup> Wessler stated that, on the contrary, involvement of the upper lobe is more frequent.

<sup>17</sup> Holman, E., Weidlein, I. F., and Schlueter, S. A. A Method for the Experimental Production of Lung Abscess, *Proc Soc Exper Biol & Med* **23** 266, 1926.

are embolic in origin (Mason<sup>18</sup>), and (3) the occurrence of fatal postoperative embolism (Capelle<sup>19</sup>)

There seems to be no need for controversy as to the possible occurrence of postoperative pneumonia or abscess of the lung of embolic origin. Following the breaking off of a piece of infected material and its lodgment in the lung, infarction and necrosis of infected tissue may frequently occur.

The statement that just as many pulmonary complications arise after local anesthesia when the cough reflex is apparently not depressed seems, on the surface, to eliminate anesthesia as an important factor and to support the embolic theory. Such cases are reported by Porter,<sup>20</sup> Simpson and Noah<sup>21</sup> and Warthin,<sup>22</sup> while in 202 cases collected by Moore,<sup>6</sup> 39, or 19.3 per cent, of the operations were done under local anesthesia. The use of local anesthesia in these cases does not, however, warrant the assumption that the subsequent abscess of the lung was embolic in nature. Most interesting in this connection is the recent work of Ochsner and Nesbit<sup>23</sup> in which is shown the fallacy of the theory that local anesthesia, because it is limited to the pillars of the fauces, does not interfere with the protective mechanism of the respiratory tract. These authors said that in more than 600 cases of bronchography, performed according to the "passive" technic, aspiration into the tracheobronchial tree occurred following the anesthetization of the pharynx. In a series of five cases of tonsillectomy done under local anesthesia, Ochsner and Nesbit found that when iodized oil—40 per cent was administered to the patients with instructions to swallow it, it could be fluoroscopically demonstrated that the oil passed into the trachea and bronchi instead of into the esophagus. These observations led them to conclude that every patient on whom tonsillectomy is performed under local anesthesia, may aspirate some of the material which enters the pharynx during the time of the operation. They stated the belief that the development of an abscess is chiefly dependent

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18 Mason, E. C. Blood Coagulation. The Production and Prevention of Experimental Thrombosis and Pulmonary Embolism, *Surg Gynec Obst* **39** 421 (Oct.) 1924.

19 Capelle, W. Einiges zur Frage der postoperativen Thromboembolie, *Beitr z klin Chir* **119** 485, 1920.

20 Porter, W. B. Pulmonary Abscess Following Tonsillectomy Under Local Anaesthesia, *Virginia M Monthly* **47** 606 (March) 1921.

21 Simpson, J. R., and Noah, H. G. Report of Two Cases of Lung Abscess Following Tonsillectomy Under Local Anaesthesia in Tubercular Subjects. *Pennsylvania M J* **23** 332 (March) 1920.

22 Warthin, A. S., quoted by Frank, I. On Lung Abscess as a Sequel to Tonsillectomy, *Laryngoscope* **27** 474 (June) 1917.

23 Ochsner, A. I., and Nesbit, W. Pulmonary Abscess, *Arch Otolaryng* **6** 330 (Oct.) 1927.

on the character of the aspirated material and on the retention of the protective cough reflex which Chevalier Jackson has aptly termed the "watch dog of the lung"

#### GENERAL EXPERIMENTS ON ASPIRATION

The extensive clinical evidence in favor of the aspiratory theory as a cause of abscess of the lung following tonsillectomy has led to a great deal of experimentation to substantiate this belief. As forerunners to the actual production of experimental abscess of the lung by this method, the concurrent studies by Lemon<sup>24</sup> and Hoelscher<sup>25</sup> on aspiration in dogs under general anesthesia are of special interest.

Lemon introduced various substances into the cheek of the dog's mouth by dripping them at a rate not much in excess of that at which saliva is produced. His experiments were conducted under ether anesthesia. An attempt was made both in the administration of the anesthetic and in the posture of the animal to simulate as nearly as possible the operative technic on human beings. He found that (1) placing the subject on an inclined plane increases the risk of extensive aspiration of mucus from the mouth into the lower respiratory passages, (2) this is lessened as the plane passes through the horizontal to a decline, and vanishes when a Trendelenburg position is reached, (3) in all other postures the dogs aspirate into the lower passages or into the depth of the lungs, especially the lower lobes, regardless of whether the head is in a straight line with the body and muzzle up or whether the head is held to one side. The dangers are increased when light anesthesia is employed, when the animal struggles, breathes stertorously, swallows or vomits. The material used in these experiments apparently played no significant rôle, as various opaque substances in variable amounts were carried upward against gravity and into the trachea and bronchi. He also stated the belief that infection about the upper air passages is an important consideration in all operations requiring general anesthesia, for bacteria that had been placed in the mouth (*Bacillus prodigiosus*) as well as organisms the normal habitat of which is the mouth, were obtained from the lung tissue. He concluded from these experiments that postoperative pulmonary infection may be explained, in part at least, as a result of infection carried to the lung in oral secretions, which have been aspirated by the force of the air current created when the chest expands in persons whose protective mechanism has been disturbed.

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<sup>24</sup> Lemon, W. S. Aspiration. Experimental Study, Arch Surg **12** 187 (Jan) 1926.

<sup>25</sup> Hoelscher, R. Experimentelle Untersuchungen ueber die Entstehung der Erkrankungen der Luftwege nach Aethernarkose, Arch f klin Chir **57** 175, 1898.

The work of Hoelscher on animals parallels that of Lemon. In corroboration of this experimental data, Myerson's<sup>10</sup> clinical observations are of great importance. He examined 100 patients bronchoscopically immediately following tonsillectomy performed under light anesthesia. Twenty-two retained the cough reflex, of these, 18 had no blood or mucus in the tracheobronchial tract and 4 did. Of the remaining 78 who did not cough during the operation, although they retained the laryngeal reflex, in only 6 was the tracheobronchial tract free from blood or mucus. According to Myerson, the preservation of the laryngeal reflex does not assure the occurrence of cough when the pharyngeal contents come into contact with the larynx, trachea or bronchus. The mixture of blood with mucus and saliva may not induce a sufficient stimulus to set up a cough reflex. On the other hand, anesthesia deep enough to abolish the cough reflex readily permits aspiration of mucus into the tracheobronchial tract.

#### UNSUCCESSFUL EXPERIMENTAL STUDIES IN ASPIRATION

The earliest attempts at the experimental production of abscess of the lung by aspiration were made by Aschner.<sup>1</sup> In conjunction with his studies on the pathologic changes in abscess of the lung he investigated this question in dogs by insufflating intratracheally pieces of infected tonsils, adenoid tissue, pus from cases of abscess of the lung and cultures of anaerobes. All his results were negative. Lambert and Miller<sup>26</sup> introduced anaerobic bacteria intratracheally into monkeys without the production of abscess. Scarff<sup>27</sup> opened the chest of dogs and injected 1 cc of semisolid agar containing virulent pneumococci into the center of a pulmonary lobe. Under fluoroscopic guidance, he also injected agar which contained virulent streptococci, staphylococci, sputum from clinical cases of abscesses of the lungs and organisms recovered from the nasal discharge and from the lungs of dogs that died from distemper. He stated that in all of the experiments he failed to produce chronic suppuration of the lung even when he injected enormous quantities and at frequent intervals. The preliminary injection of boiling water through the wall of the chest into the center of a lobe to produce necrosis and the occlusion of the bronchus with foreign bodies failed to cause a chronic infection in the lung even after organisms were introduced as previously described.

Schlueter and Weidlein,<sup>3</sup> in an attempt to produce pulmonary suppuration by aspiration, carried out a series of fifteen experiments on dogs (under ether anesthesia and morphia), employing the broncho-

<sup>26</sup> Lambert, A. V. S., and Miller, J. A. Abscess of the Lung, *Arch Surg* 8: 446 (Jan) 1924.

<sup>27</sup> Scarff, J. E. Pulmonary Blood Pressures. An Experimental Study. *Arch Surg* 12: 591 (Feb) 1926.

scope for the purpose of introducing various substances directly into the bronchi, but even by such methods none of the dogs developed any pulmonary lesions

#### SUCCESSFUL EXPERIMENTAL PRODUCTION OF ABSCESS OF THE LUNG BY ASPIRATION

The previous failures to produce suppuration of the lung by aspiration led to the investigations by Kline,<sup>28</sup> Smith<sup>29</sup> and Allen,<sup>30</sup> who reported their results in 1927. Kline, employing material from dental caries and pyorrhea alveolaris containing spirochetes and fusiform bacilli, claimed to have produced pulmonary gangrene in rabbits by insufflation. Smith also reported the production of abscesses in mice, guinea-pigs and rabbits by the intratracheal inoculation of materials scraped from the alveolar border of the teeth of patients suffering from moderate severe pyorrhea. Thirty per cent of his animals remained well, 50 per cent died from pneumonia and 20 per cent developed pulmonary abscesses. Smears and cultures from these abscesses showed the same organisms as those used in the injection material. Although grossly the abscesses produced were connected with a bronchus, none was described as bronchiectatic. As a matter of fact, histologic studies of these lesions are not reported.

Smith's conclusions were that the aspiration of infected material from the teeth and tonsils in all probability accounted for the greater number of pulmonary abscesses, and that a small number might result from infected material aspirated from the upper respiratory tract.

Following the technic of Smith, Allen was unable to produce either abscesses of the lung or pneumonia. He attributed his negative results to the supposition that spirochetes found in the upper respiratory tract in normal persons, together with the cocci and fusiform bacilli present in the material used for injections, were killed by a fifteen minute exposure at room temperature. By altering his technic he succeeded in obtaining what he interpreted as abscess of the lung in three of fifteen dogs. His conclusions were that obstruction of the bronchus plays a dominant rôle in the formation of experimental aspiratory abscess of the lung, and he also ascribed the greatest significance to the development of the "multiple abscesses" in the dogs, because clinically most patients exhibit multiple lesions rather than a single abscess with cavity.

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28 Kline, B. S. Experimental Gangrene, *J. Infect. Dis.* **32** 481 (June) 1923, Spirochaetal Pulmonary Gangrene, *J. A. M. A.* **77** 1874 (Dec. 10) 1921.

29 Smith, D. T. Experimental Aspiratory Abscess, *Arch. Surg.* **14** 231 (Jan.) 1927.

30 Allen, D. S. Etiology of Abscess of the Lung, *Arch. Surg.* **16** 179 (Jan.) 1928.

It seems to me, however, that the presence of single or multiple abscess is dependent on the number of widely separated foci simultaneously infected and followed by abscess formation. It is also probable that the multiple abscesses seen in human beings are due to the spread of the infectious material from bronchus to bronchus as a result of persistent coughing which is present in the earliest stage of the disease. This mode of dissemination is strikingly exemplified in acinous phthisis.

#### PERSONAL OBSERVATIONS

In the further elaboration of the aspiratory theory I carried on experiments in an effort to reproduce this condition in dogs. A series of twenty-seven dogs was employed in the investigation. These animals were first subjected to section of both recurrent laryngeal nerves. A period of several days was allowed to elapse in order to permit the healing of the preliminary operation. Sections of these nerves, as subsequently shown, had apparently no effect on the outcome of the experiments, as negative results were in the preponderance. The dogs were narcotized by the injection of iso-amyl-ethyl barbituric acid intraperitoneally in order to eliminate ether anesthesia as a factor in the production of pulmonary congestion.

The essential object in this study was to establish the fact that the aspiration of bacteria was responsible for the production of suppuration irrespective of any trauma of the upper respiratory tract. With this in mind, 0.5 cc. of twenty-four hour old broth culture of bacteria grown on Noguchi mediums, obtained from the sputum of patients suffering with abscess of the lung, was injected into the bronchus of the lower lobe of the lung of a dog by means of a bronchoscope. The twenty-four hour cultures contained spirochetes, fusiform bacilli, streptococci and staphylococci and were employed in most of the experiments. Before this cultured material was injected, from 1 to 2 drops of fresh, purulent sputum from the same patient from which the organisms had been obtained originally were added to make up the final 0.5 cc. used. Mixed cultures were used because most abscesses of the lungs contain a multiplicity of bacteria. Whenever single strains of organisms (streptococci) were employed, the dogs developed either pneumonia or nothing at all. Of 20 dogs injected via the bronchoscope, 2 (dogs 4 and 5) developed single encapsulated abscesses of the lower lobes, 1 (dog 467) several abscesses, two in the lower lobe and one in the upper lobe of the right lung, a fourth dog (dog 77) had a suppurative pneumonitis, and a fifth (dog 87) presented an involvement of the lower lobe characterized by a large scar within the lobe, which was adherent to the diaphragm. The appearance of this lesion was similar to the abscesses of the lower lobes which had been obtained in dogs 4 and 5, except that it looked healed. In this experiment the same cul-

tures were used as employed in dogs 4 and 5, with the exception that they were forty-eight hours old and probably less virulent. This may also have accounted for the rapid healing.

#### TECHNIC

The technic as employed by Dr. Sidney Yankauer and members of his staff who assisted in this work was as follows:

Dogs were employed in these experiments exclusively. They were first anesthetized with a 2 per cent solution of iso-amyl-ethyl barbituric acid, intraperitoneally. From 3 to 4 cc of such solution, per kilogram of body weight, was administered to each dog, which induced sleep within fifteen minutes. A bronchoscope was introduced into the animal as far into the divisions of the main bronchi as possible, then a small cannula, 1.5 mm in diameter, but long enough to reach well beyond the bronchoscope, was introduced and advanced as far into the bronchioles as it would reach. To this cannula a glass syringe was attached, by means of which 0.5 cc of various bacterial mixtures were injected. The material used for injection consisted of 0.5 cc of a mixed culture of bacteria, containing streptococci, staphylococci, fusiform bacilli and spirilli, grown on Noguchi mediums for twenty-four hours. This culture was derived from the sputum of a patient suffering from chronic abscess of the lungs.

#### PROTOCOLS

*Experiment 1*—May 25, 1926. Dog 1, weighing 8 Kg., was given 20 cc of a 2 per cent solution of iso-amyl-ethyl barbituric acid intraperitoneally. Following the injection the dog manifested a marked febrile reaction and died within four days. Autopsy showed pneumonia involving all the lobes. Microscopic section also showed an extensive hemorrhagic pneumonia.

Five-tenths cubic centimeter of the same culture as that used in dog 1, except that it was mixed with 0.5 cc of blood removed from the femoral vein, was injected simultaneously into dog 2. Following this injection, the dog slept profoundly for twenty-four hours. Between May 25 and June 5, the temperature ranged between 101.4 and 103 F. A roentgenogram taken on May 30 showed a pneumonic infiltration in the lower lobe of the right lung. On June 5, the dog was killed. Autopsy revealed an organizing pneumonia. Microscopic section corroborated the process.

Dog 3, weighing 8.5 Kg., was given injections in the same manner as dog 2. He reacted with a temperature ranging between 101 and 103 F. A roentgenogram taken on May 30 showed a pneumonic involvement of the lower lobe of the right lung. On June 7 the animal was killed. On microscopic section, hemorrhagic pneumonitis and areas of productive pneumonia were observed.

*Experiment 2*—May 28, 1926. Dog 4, weighing 8 Kg., was given 30 cc of iso-amyl-ethyl barbituric acid intraperitoneally. Two days beforehand the recurrent laryngeal nerves were cut so as to prevent the dog from barking. Five-tenths cubic centimeter of mixed culture from a case of abscess of the lung, plus some fresh pus obtained from the same case, were mixed in a syringe and introduced into the bronchus by the technic previously described. On May 30, the temperature of the dog rose to 103 F. The dog coughed on the slightest exertion and was extremely sick and inactive. Physical examination showed an area of bronchial breathing over the lower lobe of the right lung. Roentgen examination showed an

infiltration in the lower lobe of the right lung in the region into which the mixture of bacteria and fresh pus had been introduced. On June 5, eleven days after injection, the dog was killed. Autopsy showed a swollen lower lobe of the right lung which was widely adherent to the diaphragm. Within this lobe a hard nodule, 4 cm in diameter, was felt, which on section proved to be an encapsulated solitary abscess. The capsule was composed of thickened, fibrous connective tissue which merged with the adhesions to the diaphragm. It was impossible to trace any direct connection between the abscess and a bronchus. It seemed to have been completely walled off. Microscopic section showed a fairly large abscess with an extensive area of central necrosis, in which polymorphonuclear cells, mononuclears, red blood cells and various broken down cellular elements were scattered. The necrotic mass was surrounded by a zone of granulation tissue which in turn was enclosed by a fibrous capsule of connective tissue, sending prolongations into the enclosed granulation tissue. Outside the fibrous capsule the lung showed an extensive pneumonitis with sections of collapse induration. The pleura was extensively thickened (fig 1).

*Experiment 3*—May 28, 1926. Dog 5, weighing 8 Kg, was given 30 cc of iso-amyl-ethyl barbituric acid intraperitoneally (two days after section of the recurrent laryngeal nerves), twenty minutes later the dog was profoundly asleep. Five-tenths cubic centimeter of culture plus fresh pus from the same case as used in dog 4 was employed. This mixture was introduced into the bronchus of the lower lobe of the left lung, in the same way as in the other experiments. The following day the dog was still asleep and extremely sick. The temperature ranged between 102 and 103 F in the afternoons for the next week. Cough began on the third day after inoculation. The dog was killed on June 8. A roentgenogram showed an infiltration in the lower lobe of the left lung. Autopsy showed an enlarged lower lobe, in the lower end of which there was a hard, nodular mass, from 3 to 4 cm in diameter. Section showed a central area of necrosis, and the cavity surrounded by a tremendous mononuclear infiltration interspersed with fibroblasts, which arose from the surrounding fibrous capsule already formed beyond the necrotic area. Surrounding this capsule was an extensive hemorrhagic pneumonia.

*Experiment 4*—June 19, 1926. Injections of 1 cc of culture of mixed streptococci plus fresh pus were made into dogs 68, 69 and 71, after the dogs had first been subjected to section of the recurrent laryngeal nerve. All three dogs succumbed the following day with an extensive hemorrhagic pneumonia.

*Experiment 5*—June 29, 1926. Mixed cultures, including fresh purulent material, were injected into dogs 84, 85, 86 and 87, the same technic being employed. Dog 84 was killed on July 15 and showed normal lungs. Dog 85 was killed on July 7 and showed normal lungs. Dog 86 was kept alive until September 29, at which time reinjections of mixed cultures were made, he was killed on October 15. Autopsy showed normal lungs. Dog 87 was killed on July 13. Autopsy showed a thickened lower lobe of the left lung with marked adhesions to the diaphragm. Microscopic section showed scarring and fibrosis of the lung, the scar tissue leading from the diaphragm into the superimposed lung. It was impossible to state whether or not I was dealing with a healed abscess of the lung. The general appearance was suggestive, as the section resembled areas seen in the dogs with actual abscess of the lung.

*Experiment 6*—Sept 13, 1926. Injections of mixed cultures from cases of pulmonary abscess were made into dogs 73, 75, 77 and 78 on the same day, by means of the same technic. There were no spirochetes in these cultures, only anaerobic and aerobic streptococci. Dog 73 died on September 14 with extensive



hemorrhagic pneumonitis Dog 75 survived and was killed on October 14, normal lungs were found Dog 77 was killed on September 24 Histologic section showed evidence of a chronic pneumonitis and foci of suppurative pneumonia Dog 78 remained alive, and on September 28 reinjections of a mixed culture of purulent material were made This injection, as in some of the other experiments, was followed by a rise in temperature, which gradually subsided The dog remained



Fig 1—Extensively thickened pleura, below the abscess

well On October 13, injections were again made, with negative results On October 25, intrabronchial injections of 0.5 cc of bile were made into the same animal, a control for other experiments in which mixed cultures of streptococci plus bile were used for injection The bile was used with the idea of reducing local resistance The dog was finally killed on November 18 Histologic sections showed foci of hemorrhagic pneumonia and areas of interstitial pneumonia crowded with histiocytes containing foreign particles

*Experiment 7*—Oct 25, 1926 Injections of 0.75 cc of mixed culture plus 0.2 cc of diluted bile were made into dogs 254 and 255. These dogs developed pneumonia followed by complete recovery.

Five-tenths cubic centimeter of mixed culture plus 0.2 cc of diluted bile were injected simultaneously into dog 253, he was killed on November 16. Autopsy showed extensive swelling of the lower and middle lobes of the right lung, which were glued together by an interlobar exudate. Microscopic section showed acute and chronic pneumonitis. In certain areas productive pneumonia was also found. Cultures yielded a pure strain of anaerobic streptococci.

*Experiment 8*—Dec 4, 1926 A culture of anaerobic streptococci, recovered from dog 253, plus 0.2 cc of dilute bile, were injected into dogs 492, 493 and 494. Twenty-four hours later all three dogs were found dead. Autopsy showed extensive hemorrhagic pneumonia in each case.

*Experiment 9*—Jan 3, 1927 Five-tenths cubic centimeter of streptococcus culture removed from dog 253, was injected into dog 487. The dog was killed on January 12. Autopsy showed nothing abnormal in the lungs.

An injection of 0.5 cc of mixed culture plus fresh sputum from a case of abscess of the lung was made into dog 489. The injection was followed by death on January 5 from pneumonia.

*Experiment 10*—Feb 19, 1927 An injection of 0.5 cc of mixed culture plus fresh sputum was made into dogs 467 and 468. Dog 468 died from pneumonia. Dog 467 lived for seven days. After the injection he became ill and began to lose weight. On the sixth day he showed a marked dyspnea, cough and emaciation. He was killed on the seventh day. At autopsy a foul-smelling effusion was found in the right side of the chest. The left side of the chest contained no fluid. Examination of the lungs showed a large abscess in the lower lobe of the right lung, which had broken through into the pleura and was responsible for the foul effusion. A small abscess was also present in the upper lobe of the right lung. Microscopic examination of the lobe of the right lung showed two large abscesses, one next to the other, separated by a pneumonic area of consolidation. Each of the abscesses was surrounded by an extensive polymorphonuclear exudate, at the periphery of which was a fibrin net enmeshing polymorphonuclear cells and cocci. The necrotic central area of the abscess held numerous clumps of bacteria. The bronchi within this area were partly destroyed, their walls necrotic, the ciliated epithelium scattered and their lumina filled with a fibrinous exudate containing scattered polymorphonuclear cells in the center. The entire picture was that of a severe destruction of lung and bronchi (fig. 2).

#### SUMMARY OF PATHOLOGIC OBSERVATIONS

It is obviously impossible to compare the pathologic changes as described by Aschnei in abscesses of the lungs in human beings, with those seen in the experimentally induced abscesses reported. On the one hand, in Aschnei's material from human beings the pulmonary changes were of three or more years' duration. In the dogs the abscesses produced were characterized by a process of destruction which was rapidly followed by an attempt at repair. This was evidenced by the presence of a capsule of connective tissue about the abscesses in two of the dogs as early as the eleventh day. These abscesses were walled off and microscopically showed direct communication with the small bronchi.

A summary of the protocols showed that eight of the dogs that received injections recovered and remained well, thirteen succumbed to pneumonia, three developed pulmonary abscesses and one suppurative pneumonitis. Dog 87 probably showed the results of organizing pneumonitis. As determined by roentgenograms and confirmed by histo-



Fig 2—Destruction of the lung and bronchi, *A*, small bronchiole opening into the abscess cavity

logic study, the abscesses appeared to develop as a primary diffuse pneumonitis with progressive diminution in the size of the pneumonic area until nothing but a small infiltration remained which, at autopsy, proved to be an abscess. Clinical as well as the experimental observations also attest to the fact that a pneumonic infiltration always precedes

the development of an abscess of the lung resulting from the aspiration of bacteria intrabronchially

Histologic sections of the lungs of dogs 4 and 5, which were killed on the eleventh day of their illness, showed an abscess surrounded by extensive granulation tissue and fibrous bands which formed a well defined capsule. In dog 467, which died on the seventh day of the illness, there was a ruptured abscess in the upper lobe of the right lung. The lower lobe of the right lung was swollen, and histologically showed a large central area of necrosis. The larger bronchi within the necrotic tissue were filled with a fibrinopurulent exudate. The walls of the bronchi were necrotic, their mucosa denuded and the accompanying blood vessels thrombosed. Many of the smaller bronchi, alveolar passages and sacs were completely destroyed. The visceral pleura was greatly infiltrated and in parts thickened by granulation tissue.

Cultures from the abscesses of dogs 4 and 5 yielded streptococci which at first grew anaerobically only and subsequently aerobically, the spirochetes and fusiform bacilli having entirely disappeared. There was no fetor. The smears from dog 467 presented a mixture of streptococci and gram-positive bacilli but no spirochetes<sup>31</sup>. The disappearance of the spirochetes raises the question as to whether they were sufficiently viable before injection even though, microscopically, evidence of their motility was present, or whether the bactericidal properties of the lungs of the dogs were sufficiently strong to dispose of them. In Allen's dogs, with the exception of the one in which both the bronchus and the artery were ligated, a similar experience is recorded, seemingly pointing to the explanation that the lungs of the dogs are easily capable of disposing of these comparatively saprophytic organisms.

#### COMMENT

A survey of the literature on experimental abscess of the lung following tonsillectomy still presents two theories of the mode of formation, embolism and aspiration. The proponents of the embolic theory have produced experimental abscesses by introducing foreign bodies into the circulation with the production of an individual embolic abscess. These investigators claim that embolic abscesses are usually single, which is contrary to the general experience as seen at the autopsy table. It is only when a large vessel is occluded by a large embolus which does not readily break up that an extensive single area of necrosis follows. Even admitting the possibility of the occasional embolic origin of an abscess following tonsillectomy in human beings,

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31 No cultures were made in this case because the autopsy was not done under sterile conditions.

it does not necessarily follow from the work of these investigators that all abscesses are to be explained on this etiologic basis. The occurrence of a single abscess is not an absolute criterion of their embolic nature. The results with intrabronchial insufflation of mixed cultures in the production of single abscesses refute such contentions.

It is significant from all the experimental work in this field that no one has been able to produce chronic abscess of the lung with the pathologic picture described by Aschner in human beings. The abscesses produced by means of emboli were designated by their authors as parenchymatous. Those induced by Smith were described as "walled off and in connection with a bronchus," but not bronchiectatic. Even the abscesses produced by Allen, which give the impression of being areas of suppurative pneumonitis rather than true abscesses of the lungs, were described as "remote from the main bronchus," the infectious material seeming to have been trapped in smaller bronchioles. There is nowhere mention of bronchiectatic abscess.

It is of significance that abscesses of the lungs have been reproduced in dogs, as well as in smaller animals, by aspiration without previous trauma to the respiratory tract, and that in the experiments no more than 0.5 cc. of mixed culture was necessary for this purpose. The probable factors in the successful experimental production of such abscess in the dogs in contrast to previous failures of some investigators are to be found in the imprisonment of bacteria in the bronchi as suggested in Allen's experiments, and possibly in the abolition of the cough reflex through the administration of iso-amyl-ethyl barbituric acid as an anesthetic which induced sleep for twenty-five hours. The sleep prevented expulsion of the infectious material and enabled the bacteria to multiply. The repeated presence of pneumonia, resulting in suppuration both in the dogs reported and in those of Allen, and the presence of single and multiple abscesses show that aspiration can be the causative factor of abscesses following tonsillectomy.

If the aspiration theory of abscess following tonsillectomy is examined from the point of view of its development, it is probably as follows. Aspiration of bacteria producing pneumonia constitutes the first stage. With the occurrence of the pneumonitis and cutting off of the active circulation, diminished local tissue resistance ensues. The rapid increase of bacteria, many of which are proteolytic,<sup>32</sup> together with the toxins and inflammatory by-products (enzymes, etc.) leads to the liquefaction of the tissue involved and the formation of abscesses. Other areas of the lungs may become infected by organisms introduced from the original necrotic area through coughing. Pneumonic areas

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32 Many strains of streptococci cultivated on Noguchi mediums isolated from cases of abscess of the lung, which were employed in the experiments, showed definite proteolytic properties *in vitro*.

arise about these abscess cavities, which may serve as rich reservoirs for the maintenance of the numerous types of bacteria as well as of the spirochetes usually found. It is a well known fact that when spirochetes are not recovered in the sputum, they are invariably found in the edges of all abscess cavities and are in all probability secondary invaders. These pneumonic areas in their turn break down and lead to an extension of abscess formation. Simultaneously, however, as in all other inflammatory processes, destruction is associated with repair. In the process of destruction, the smaller bronchi involved in the abscess completely disappear, as seen in the sections presented, and the surrounding pulmonary tissue shows interstitial inflammation. This leads to the formation of connective tissue which later shrinks, drawing with it and stretching the partially destroyed and dilated, but more resistant, bronchi. Such a process with the consequent stenosis and kinking of remaining bronchi may in the course of events lead to actual bronchiectatic cavity formation. Should the process of destruction proceed more rapidly, the abscess becomes more extensive. In human beings, Aschner stated that, "About the abscess cavity the bronchial branch leading into it and the bronchus passing out of it, the lung tissue is converted into a firm, indurated mass showing dense bands of connective tissue separating grayish-yellow, raised areas. When the main lobe bronchus is the site of the abscess, the whole parenchyma shows the fibrotic lesion."

It is obvious from this description that the lung tissue, after several years of destruction and repair, becomes shrunken until practically a fibrous mass containing bronchiectatic cavities and a large bronchus belonging to the lobe is all that is left. The conception that the initial process may be a circumscribed bronchial lesion leading to stenosis and subsequent distal dilatation with the formation of a primary bronchiectatic cavity deserves consideration. Such a conception, however, seems to gain its origin from a study of the end-stages alone. The initial stages in abscesses in dogs, on the contrary, if these may be taken as criteria, in a study of lesions in human beings suggest the pneumonic origin. This is frequently also seen clinically. It is repeatedly confirmed by the roentgen rays and is associated with the expectoration of foul-smelling sputum containing spirochetes, fusiform bacilli, streptococci, etc. Such a pneumonic process, which may even go on to partial necrosis, may subside and completely heal within from three to six weeks in 30 per cent of cases (Wessler<sup>11</sup>). In the remaining cases, destruction of lung tissue proceeds. The persistent cough which disseminates the infectious material into contiguous bronchi with the usual sequence of events, i.e., bronchopneumonia, necrosis of pulmonary tissue and bronchial elements, fibrosis and dilatation of the remaining bronchi, completes the cycle which may finally end with the production of the bronchiectatic cavities.

## CONCLUSIONS

1 A consideration of the pathogenesis of pulmonary suppuration following tonsillectomy has been presented from the points of view of the embolic and aspiratory hypotheses

2 Results of experimentations on animals as well as clinical experience point to the fact that while embolic abscesses may occur, they are exceptional. The greater amount of evidence is in favor of aspiration as the mode of production of suppuration of the lung following operations on the upper respiratory tract

3 Three of twenty-seven dogs that received, through the bronchoscope, 0.5 cc of mixed cultures of bacteria recovered from the sputum of patients with abscesses of the lungs following tonsillectomy, developed abscesses with cavities, one developed pulmonary suppuration and a fifth presented evidence of a healed suppurative process in the lower lobe of the left lung—14.8 per cent of pulmonary suppuration

4 Suppuration following tonsillectomy, characterized by Aschner as bronchiectatic, extrabronchial abscess and suppurative pneumonitis, have been found by him in specimens of the lungs studied from two to five years after tonsillectomy. While the last two forms have been obtained by me experimentally, bronchiectatic abscess could not be produced by this method in dogs. The reason suggested for this failure is to be found in the rapid tendency on the part of abscesses experimentally produced in dogs to go on to healing. Encapsulation of the abscess was already observed as early as the eleventh day

5 The development of pulmonary abscesses in dogs is first manifested by the presence of pneumonia as demonstrable by the roentgen rays. This is comparable to the condition seen in the human being in the earliest stages following tonsillectomy. Subsequent stages of this condition, as studied histologically in the dogs, are characterized by the occurrence of necrosis within the pneumonic area and in cavity formation. This may persist or go on to healing

6 If results obtained in dogs may be translated to the conditions occurring in man, it is suggested that following aspiration of infectious material from the upper respiratory tract, the current of events is as follows: (1) pneumonitis, (2) necrosis and cavity formation, (3) healing or persistence of the primary abscess with the formation of secondary bronchiectasis

# INSULIN IN ACROMEGALIC DIABETES \*

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I recently reported a case of hyperpituitary disease with diabetes in which the efficacy of insulin was found to be impaired to a marked degree<sup>1</sup>. Nearly all other authors have claimed, however, that acromegalic diabetes does not differ from pancreatic diabetes in the patient's response to treatment with insulin. I referred to some of them (John,<sup>2</sup> Hetzel,<sup>3</sup> Sachs and MacDonald,<sup>4</sup> and Blum and Schwab<sup>5</sup>) and demonstrated that the evidence presented by them was inadequate to prove their claim.

Yater,<sup>6</sup> in an article published simultaneously with mine, again attempted to show that insulin is in every respect as effective in acromegalic diabetes as it is in the pancreatic type. He reported three cases and cited Colwell,<sup>7</sup> among others, in support of his contention.

It is my purpose here to show that a critical analysis of Yater's and Colwell's results and of the figures they publish does not yield such an interpretation. On the contrary, it is easily demonstrated that their results support the opposite contention. The apparent importance of these articles, Yater's written from the Mayo Clinic and Colwell's from Woodjatt's clinic, demands all the more a critical review.

It has been demonstrated by many experimenters, some of whom I quoted, that injections of pituitary extract exert an antagonistic action on insulin. This fact suggests that the diabetes of acromegaly may be the result of a similar antagonism exerted by excessive pituitary secretion on normally secreted endogenous insulin, this, in turn, leads to

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1 Ulrich, H. The Antagonism Between Insulin and Pituitary Extract. Its Demonstration in a Patient with Acromegaly, *Arch Int Med* **41** 875 (June) 1928

2 John, H. J. Spontaneous Disappearance of Diabetes, *J A M A* **85**: 1629 (Nov 21) 1925

3 Hetzel, K. S. Glycosuria in Acromegaly, *Lancet* **1** 440 (Feb 27) 1926

4 Sachs, E., and MacDonald, M. E. Studies in Experimental Pituitary and Hypothalamic Lesions, *Arch Neurol & Psychiat* **13** 335 (March) 1925

5 Blum, L., and Schwab, H. Diabete acromegalique et insuline, *Compt rend Soc de biol* **89** 195 (June 8) 1923

6 Yater, W. M. Acromegaly and Diabetes, *Arch Int Med* **41** 883 (June) 1928

7 Colwell, A. R. The Relation of the Hypophysis to Diabetes Mellitus, *Medicine* **6** 1, 1927



the expectation that an additional supply of insulin, given by the parenteral route, will be partly or wholly ineffective. That was found to be true in the case that I reported.

The patient has died since the report was made. The antemortem diagnosis of pituitary neoplasm was confirmed at necropsy. A large pituitary adenoma was found.

During the course of his illness the patient had two attacks of pronounced glycosuria and hyperglycemia. The first extended over a period of about a month and then disappeared spontaneously, the second came on nearly two years later and continued until the time of death. Insulin appeared to have little effect on the level of the blood sugar during both of these periods, as is shown by the figures and charts contained in my previous article.

In the literature I have found only one other case (Mahler and Pasterny<sup>8</sup>) that was reported for the purpose of demonstrating the relative inactivity of insulin in acromegalic glycosuria. The patient had a proved pituitary tumor. Sixty units of insulin did not affect the hyperglycemia.

Another case of apparently the same type was reported by Falta<sup>9</sup>. Here the diagnosis was doubtful, although the glycosuria, low basal metabolic rate, obesity and extremely small sella turcica suggested a hypophyseal influence. The blood sugar, before treatment with insulin was begun, was 226 mg per hundred cubic centimeters of blood. Insulin was given for a period of nine days, at first 90 units a day and later 140 and 150 units. The level of blood sugar remained high, varying during this time between 220 and 250 mg per hundred cubic centimeters.

Yater<sup>6</sup> reported six cases of acromegaly with diabetes in three of which insulin was used. His contention that acromegalic diabetes yields as readily as the pancreatic type to treatment with insulin is based on the reports of these three cases.

Table 1 is a condensation of Yater's tables illustrating his case 3. It shows that a daily dosage of 50 units of insulin was begun when the patient's blood sugar amounted to 364 mg per hundred cubic centimeters. Two days later it had come down to 250 mg, and a week later to 160 mg. It will be noted, however, that the amount of carbohydrate in the diet was greatly reduced on the day before treatment with insulin was started. The reduction of blood sugar may therefore have been caused by dietetic restriction. At any rate, it is impossible to say how much of it was effected by the dietetic change and how much by insulin. The lower portion of the table suggests that the diet had the greater

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8 Mahler, P., and Pasterny, K. *Klinische Beobachtungen über Insulinwirkung beim Diabetes mellitus*, *Med Klin* 20 337 (May) 1924.

9 Falta, W. *Ueber einen insulinrefraktären Fall von Diabetes mellitus*, *Klin Wchnschr* 3 1315 (July) 1924.

influence and may alone have been responsible for the lowering of the amount of blood sugar. It is shown that after an interval of twelve days without any insulin, the amount given was 15 units, or less than a third of that given at first, yet the blood sugar came down to 130 mg, that is to say, it was lower when 15 units of insulin were used than when 50 units were used. But here again the diet had been reduced still further, which, of itself, is sufficient to explain the additional drop in the amount of the blood sugar. It is unfortunate that estimations of blood sugar apparently were not made during the period when insulin was not given.

Another of Yater's cases (case 5) concerns a woman suffering from acromegaly, hyperthyroidism and diabetes. Her history before entrance to the hospital included reference to two attacks of diabetic coma.

TABLE 1—*The Data in Yater's Case 3*

Date, 1926	Carbohydrate in Diet, Gm	Dextrose in Urine, Gm	Blood Sugar, Mg per 100 Cc	Insulin, Units per Day
1/ 8	199	79.22	334	
1/ 9	190	135.7		
1/10	196	145.6		
1/11	170	119		
1/12	102	69.78		
1/13	100	20.41	364	50
1/14	101	3.87		50
1/15	99	6.41	250	50
1/16	101	0.95		50
1/21	102			50
1/22	100		160	50
1/24	100			
2/ 3	110			
2/ 4	73			15
2/ 7	100			15
2/ 9	54			15
2/11	54		130	15
2/12	54			15
2/17	54		147	15

Insulin was used during both of them. The patient recovered from the first attack after two days. Other details of this attack are lacking. During the second attack, she received 300 units of insulin within forty-eight hours. She awoke for half a day, but relapsed into coma. It was "decided that she had been revived from diabetic coma only to go into a state of hypoglycemic shock." Twenty grams of dextrose was administered intravenously, and the patient recovered.

After she came to the hospital, the urine contained occasional small quantities of sugar, the amount of blood sugar was relatively low, and the quantity of insulin used was small. The results, therefore, were not striking, but they indicate that insulin appeared to have little effect.

Later, a partial thyroidectomy was performed. Three fourths of the right lobe was removed. The patient died nine days after the operation.

Table 2 gives the facts regarding urinary dextrose, blood sugar and the dosage of insulin collected during the postoperative period. It will

be seen that increasing amounts of insulin, even to the huge dose of 215 units a day, did not prevent a simultaneous rise in the amount of blood sugar

Yater is at a loss to "explain the inability of insulin to affect the blood sugar" during this period. He suggests the possibility that a thyroid crisis was responsible for it, but states that a "thyroid crisis is incompatible with the histologic picture" of the thyroid gland of this patient

On the other hand, it is obvious that the figures in table 2 should not be used as evidence of the inactivity of insulin in hyperpituitary disease. They were obtained after an operation on the thyroid when the patient was about to die. These complications may have masked any effect exerted by the hypophysis. And it may be said also that all of the other observations in this case, even if they tend to support Yater's contention—which they do not—, should be barred, because the case is not one of uncomplicated pituitary disease. Hyperthyroidism

TABLE 2—*Postoperative Data in Yater's Case 5*

Date, 1927	Dextrose in Urine, Gm	Blood Sugar, Mg per 100 Cc	Insulin, Units per Day
8/13	13.5	392	20
8/14	49.7		30
8/15	87.0	350	30
8/16	84.3	400	90
8/17	124.6	400	80
8/18	58.9	426	135
8/19	64.5	454	215
8/20	27.3	500	160

has its own effects on metabolism. The present incomplete knowledge of the endocrine functions and particularly of their interrelations does not enable one to separate fully the metabolic effects of hyperthyroidism from those of a complicating dysfunction of the hypophysis. Yater sensed this when he wrote that "the patient may have been on the crest of a wave of hyperthyroidism at the time of the [attacks of] coma."

Yater's third case in which insulin was used (case 6 of his whole series) also was complicated by disease of the thyroid. Dietetic restriction reduced urinary sugar from a "moderate amount" to a trace, and the blood sugar from 206 to 165 mg per hundred cubic centimeters. Ten units of insulin was then given twice a day to remove the traces of sugar from the urine, but it is not recorded how the blood sugar was affected by the insulin. This case is, therefore, without value in this connection. In the historical record of the patient, however, one reads that before he entered the hospital he "had often taken as much as 160 units in a day without severe reaction." It would appear, then, that the case could be cited with greater propriety as proof of the hampered action of insulin than as evidence of its efficiency.

Yater reached the conclusion that both the acromegalic and the pancreatic types of diabetes are the results of the same cause, namely, an insufficient production of insulin. Yet, he qualified this conclusion by saying that in acromegalic diabetes "it is possible that enough insulin might be secreted but might be neutralized by some new substance." To this I would add that such a new substance, as Borchardt<sup>10</sup> suggested long ago, is most likely to be an excessive pituitary secretion. If it might neutralize the normally secreted endogenous insulin, it might just as readily neutralize some or all of any additional insulin injected under the skin.

In addition to his own cases, Yater referred to Colwell's paper<sup>7</sup> for support of his thesis. Colwell's article is a splendid review of the literature concerning the relation of the hypophysis to carbohydrate metabolism. The question of the efficacy of insulin in the diabetes of

TABLE 3—*The Data in Colwell's Case*

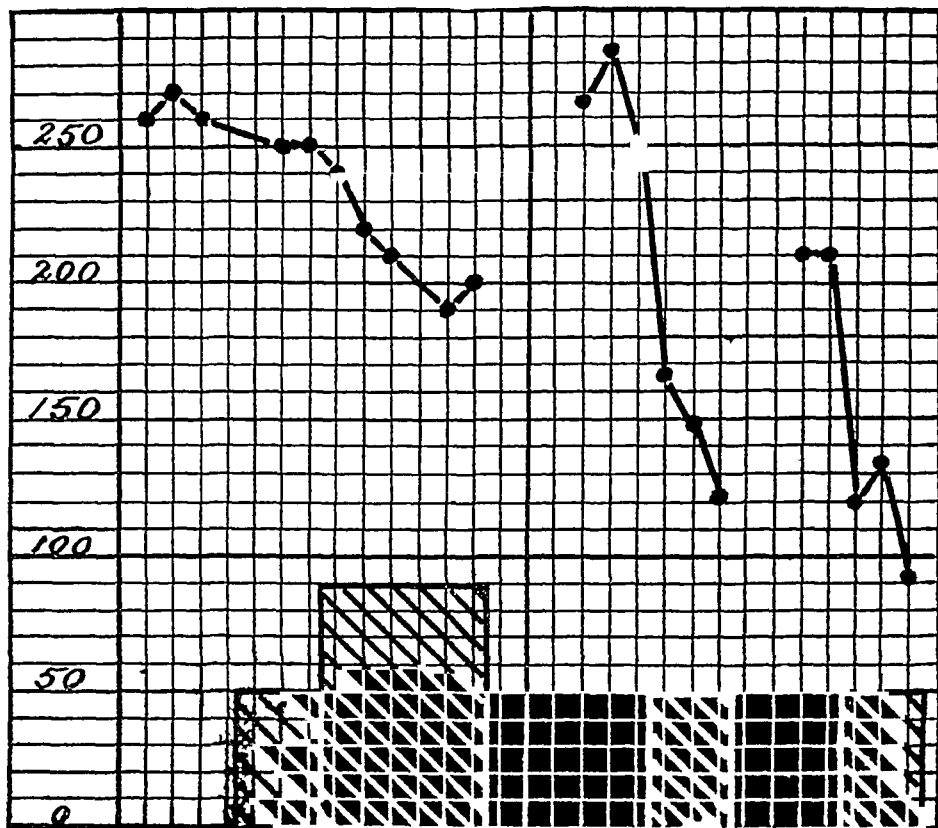
Date, 1925	Dextrose in Urine, Gm	Fasting Blood Sugar, Mg per 100 Cc	Insulin, Units per Day
3/19	37.8	260	
3/20	33.5	270	
3/21	46.6	260	
3/22	35.6		
3/23	17.0		50
3/24	20.2	250	50
3/25	16.1	250	50
3/26	15.3	240	90
3/27	14.4	220	90
3/28	10.9	210	90
3/29	2.3		90
3/30	5.7	190	90
3/31	2.1	200	90

acromegaly is included. Colwell cited four cases from the literature and added one of his own to prove that insulin affects the diabetes of acromegaly "in a manner similar to that observed in ordinary diabetes mellitus."

Table 3 gives the essential data of Colwell's case. The diet remained constant throughout the period covered by the table. Fifty units of insulin a day, which is not a small dose, effected a reduction of the amount of blood sugar from 260 to 250 mg per hundred cubic centimeters. This is practically negligible. Ninety units a day, which is a large amount, brought the amount of blood sugar down to 200 mg. I cannot agree with Colwell that these results show that insulin has acted "in a manner similar to that observed in ordinary diabetes mellitus." On the contrary, the same amounts of insulin given to patients with uncomplicated pancreatic diabetes will elicit a much greater response.

10 Borchardt, L. Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie, *Ztschr f klin Med* 66 332, 1908

This fact is shown in the accompanying chart. The curve at the left of the chart illustrates the effect of insulin in Colwell's case, the curves on the right were obtained with patients suffering from pancreatic diabetes. In all of the cases the level of fasting blood sugar had been stabilized by diet before insulin was used. The relatively minor variations in the first case of pancreatic diabetes do not contradict this statement, on the contrary, they emphasize the fact that a drop of the level of blood sugar amounting to only 10 mg per hundred cubic centimeters, which Colwell credited to insulin, is not necessarily to be



Comparison of the effects on the fasting level of glycemia produced by insulin in Colwell's case (represented by the first curve at the left of the chart) and in two cases of pancreatic diabetes (represented by the second and third curves). The hatched areas represent the amounts of insulin given in each case. The scale indicates the number of units of insulin given each day and the number of milligrams of blood sugar per hundred cubic centimeters of blood.

regarded in that light. Colwell's case varied by that amount before treatment with insulin was begun.

Fifty units of insulin a day elicited a far greater response in the patients with pancreatic diabetes than it did in Colwell's case of acromegalic diabetes. In fact, this amount was more effective in these patients than was the larger amount of 90 units in Colwell's case. Both

patients with pancreatic diabetes suffered from fairly severe insulin shock on the evening preceding the last test for blood sugar included on the chart, both received orange juice at that time. Had this been omitted, the last amount of blood sugar recorded in each case would probably have been still lower. It was neither advisable nor necessary, therefore, to carry the comparison with Colwell's case further by giving 90 units of insulin as he had done. It is evident that the difference between the curves would stand out still more strikingly, had the portion representing the effect of 90 units in Colwell's case been omitted.

Colwell's case, therefore, adds further proof that insulin is less active in cases of acromegalic diabetes. The fact that a slight reduction of blood and urinary sugar in this form of diabetes may be effected by insulin is not sufficient evidence of its adequate action, its action must be shown to be as great as it is in the average case of pancreatic diabetes. It is likely that cases of acromegaly may respond in varying degrees to treatment with insulin. The variability may depend on varying intensities of hypopituitary activity or, possibly, on other complicating influences.

Three of the four cases cited by Colwell from the literature, those of Sachs and MacDonald,<sup>4</sup> John,<sup>2</sup> and Blum and Schwab,<sup>5</sup> were discussed briefly in my previous article. They are taken up again in this paper, together with Hetzel's case,<sup>3</sup> which was not mentioned by Colwell.

Hetzel came to the conclusion that in his case "the glycosuria was identical with that of diabetes, it reacted similarly to insulin and control of the diet." This conclusion, however, does not agree with the text of the report of his case. There he stated that "insulin was increased successively to 40, 45, 50 and 60 units a day to lower this hyperglycemia [0.24 per cent], but the effect was only small, for the blood sugar fluctuated throughout the day between 0.15 per cent and 0.20 per cent." In the history of the patient appears the statement that ten months before admission, he had been treated for his glycosuria by dieting. "Insulin was also tried, but it was said to have been without effect, and the efficacy of insulin was doubtful." All evidences of diabetes finally vanished, and it may have been this fact that brought Hetzel to the foregoing conclusion. If that is so, he was misled in that he misinterpreted a spontaneous recession of pituitary glycosuria, a common occurrence, as a therapeutic effect of insulin.

The fourth case cited by Colwell was reported by Etienne and his associates<sup>11</sup>. They gave "pancreatic extract (presumably insulin)" to a patient with acromegaly and glycosuria and observed that the glycosuria was reduced. Colwell, however, seems to have overlooked the

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11 Etienne, G., Drouet, L., and Yovannovitch-Brintcheva, B. Glycosurie dans l'acromégalie, *Rev. méd. de l'est* **50** 271 (May) 1922. Etienne, G. Sur la pathogénie de la glycosurie chez un acromégalique, *Rev. neurol.* **38** 730 (June) 1922.

important statement made by the French writers that a certain amount of sugar persisted and was not affected either by the continuous action of the pancreatic extract or by increasing the dose. They believed that part of the glycosuria was pancreatic in origin and therefore amenable to treatment with insulin, and that the irreducible residue was the effect of hyperactivity of the posterior lobe of the hypophysis and for that reason was not affected by insulin. In short, they concluded that true hypophyseal diabetes could not be influenced by treatment with insulin.

Aside from this point, however, their case is open to the objections that the amount of pancreatic extract given was not stated, nor is there any record of estimations of blood sugar. Furthermore, the case was not one of uncomplicated acromegaly, but, according to the authors, presented, in addition, hypertrophy of the thyroid, hypertrophy and noninvolution of the thymus, hyperactivity of the suprarenals and ovarian insufficiency.

The case of Sachs and MacDonald<sup>4</sup> is that of a woman operated on for "acute acromegaly." The operation was followed by glycosuria which, they stated, "in no way differed from the glycosuria of a diabetic patient," and which "was furthermore controlled by the administration of insulin." Glycosuria was apparently not present before the operation, so that it must be regarded as a result of operative trauma rather than as a symptom of pituitary disease. This places the case in a different category and does not prove the efficacy of insulin in true hypopituitary glycosuria.

John's report of a case<sup>2</sup> concerns a man with acromegaly and diabetes. The blood sugar amounted to 440 mg per hundred cubic centimeters at the time of his admission to the hospital. The patient was put on a restricted diet and received 100 units of insulin a day for ten days. The blood sugar had then reached the normal level. Insulin was reduced to 20 units a day and given in this amount for about two weeks. The amount of blood sugar remained normal. Insulin was then omitted, and the daily ration of carbohydrate was raised from 100 to 120 Gm. Protein and fat, also, were increased. Despite these changes "the patient kept a normal blood sugar level until he was discharged."

John concluded that the patient was cured of diabetes as a result of the treatment. He reported the case primarily for that purpose, together with another one, with diabetes of a lesser degree, in which insulin was not used but in which the loss of carbohydrate tolerance later vanished. It is noteworthy that both were cases of acromegaly. Cures of patients with true pancreatic diabetes are exceedingly rare, the spontaneous disappearance of acromegalic diabetes is relatively common. This must lead to the conclusion that John's cases were of the latter type. It is probable that the initial dietetic restriction in his

first case lowered the amount of blood sugar to some extent and may even have been the impetus that led to the eventual restitution of carbohydrate tolerance. In this sense it may be spoken of, perhaps, as a cure, but I believe that the tendency to spontaneous recession of glycosuria, shown in many cases of acromegaly, was the important determining influence in both of John's cases.

As far as the effect of insulin in his first case is concerned, definite conclusions cannot be reached. Curtailment of diet and treatment with insulin were started at the same time, hence, as in Yater's case, their separate effects cannot be estimated. The fact that blood sugar did not increase when insulin was omitted supports the argument that it was ineffective.

Blum and Schwab,<sup>5</sup> also quoted by Colwell, gave 30 units of insulin to each of two patients, one with acromegalic glycosuria, the other with pancreatic diabetes. The responses were essentially equal. Details about the patient with acromegaly are lacking. This is unfortunate. The reader is deprived of the opportunity of making an independent interpretation of the observations in the case. If, for instance, the previously quoted writers, Sachs and MacDonald, had failed to state that their patient had developed glycosuria after an operation, but had merely reported their case as one of acromegalic glycosuria amenable to insulin, the conclusions to be drawn from it would have been decidedly different. Nevertheless, in the absence of other evidence, the case of Blum and Schwab must be accepted as being presumably one of hyperpituitary loss of carbohydrate tolerance in which insulin was effective.

It may be, therefore, that there are gradations of antagonism against insulin in different patients with acromegaly, varying from none at all, as in the case reported by Blum and Schwab, to almost complete inhibition, as in the case which I have described. Several explanations of this variability suggest themselves. It may be brought about by varying intensities of hyperpituitary activity. "Or, if it is true that pituitary tumors may give rise to glycosuria by pressure on neighboring brain centers, the simultaneous presence of such a pressure type, which may be amenable to insulin, with a hypersecretory type, would lead to varying degrees of responsiveness to treatment with insulin. Again, it is conceivable that some of the patients may develop true pancreatic diabetes, owing to exhaustion of the pancreas from constant stimulation by the pituitary hyperglycemia. Such patients may then become more susceptible to treatment with insulin."

Yater stated that "the balance of evidence at hand from a clinical standpoint certainly favors the deduction that insulin acts in acromegalic diabetes just as it does in diabetes without acromegaly." I have attempted to show that critical analysis of this evidence, including his own, fails to support such a statement. On the contrary, most of the



evidence at hand favors the deduction that insulin acts less efficiently in cases of acromegalic diabetes than it does in diabetes without acromegaly

The evidence, I believe, is sufficiently convincing to warrant the use of insulin for diagnostic purposes in cases of glycosuria that are suspected of having a hypophyseal foundation. A demonstrable failure of insulin to produce its expected and usual results should be regarded as a link in the chain of evidence leading to a diagnosis of hyperpituitary disease

# CLINICAL TYPES OF EDEMA IN THE HEART FAILURE OF CHILDHOOD\*

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A study of the clinical course of edema in nephritis, recently published by Aldrich,<sup>1</sup> prompted me to attempt a similar study of the edema associated with heart disease in children. The underlying thought in both these observations has not been to advance any new theories regarding the cause and nature of edema, but rather to add precise clinical data to the knowledge of this interesting problem.

During the past five years, I have had the opportunity of observing a large number of children with heart disease, and as these children have gone on to recovery, chronic invalidism or death, I have been impressed with the wide variations in the symptoms and signs encountered. The clinical picture of associated edema in the child with heart failure, however, has always been one of two definite types, each one running a constant course, differing only in degree.

The first type of edema is the commonly recognized dependent type, involving the dependent portions of the body almost exclusively. It appears most prominently in the lower extremities, about the sacrum, and occasionally, depending on the position of the patient, in other portions of the body. With this type of edema there are usually found ascites, marked enlargement of the liver and other evidence of cardiac failure. As a rule, these children not only suffer from their discomfort and cardiac embarrassment, but are acutely ill and frequently toxic.

The second type of edema is generalized, and I have come to term it the "nephritic type," because of the similarity of the distribution to that seen in nephritis. It appears first in the face and later becomes equally prominent in all portions of the body. In degree it is never so overwhelming as that seen in nephrosis, but it has the same generalized distribution regardless of the position of the patient. Otherwise, the clinical picture is that of a patient with heart failure, though the heart failure is seldom so severe as that found in the previous type, nor is the patient ever so acutely ill. He appears more as a convalescent patient who has outlived an acute infection and presents the usually associated pallor and poor nutrition. The urinary observations are negative with

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\* From the Cardiac Department of the Children's Memorial Hospital.

\* Read at the Society of Internal Medicine, Chicago, March 26, 1928.

1 Aldrich, C. A. A Study of the Clinical Course of Generalized Edema. J. A. M. A. 84: 481 (Feb. 14) 1925.

the exception of small amounts of albumin which are encountered no more frequently in the one type than in the other

Little has been said about the second or generalized type of edema as seen in heart failure in children Resnick and Keefer<sup>2</sup> recently commented and theorized about an edema of the face associated with myocardial insufficiency Other mention of facial edema has been made by Cohen,<sup>3</sup> Mackenzie,<sup>4</sup> Miller<sup>5</sup> and Crummer,<sup>6</sup> however, their rather casual comments do not suggest the idea that this is a true clinical entity appearing in the heart failure of childhood This is the more remarkable since generalized edema in the child with cardiac disease is not of exceedingly rare occurrence in a large service of children with heart disease

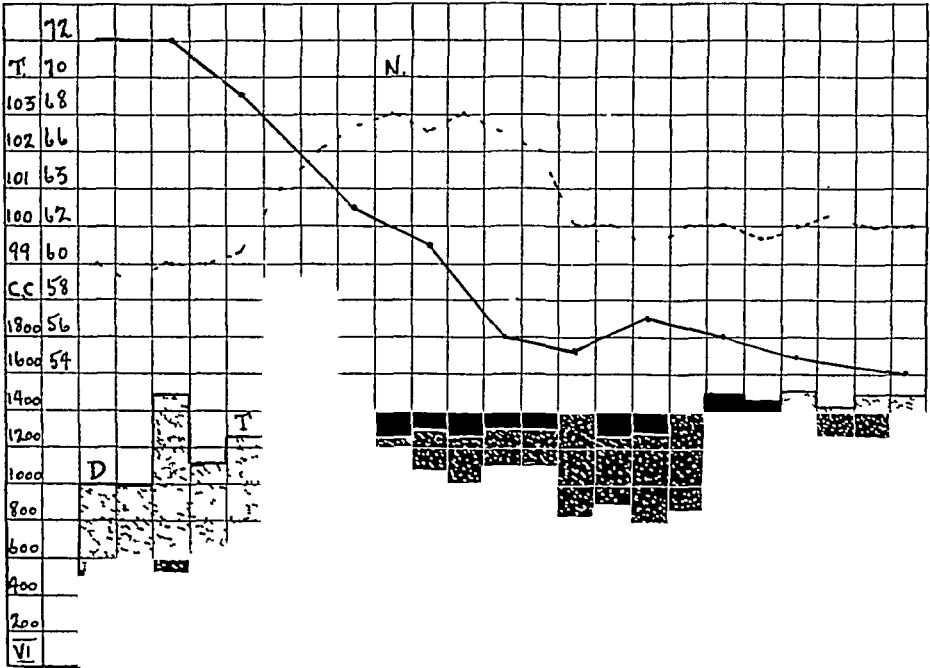


Chart 1—Generalized edema Digitalis (*D*) did not give results Elimination occurred following the administration of theobromine sodio-salicylate (*T*) A marked rise in temperature and nausea (*N*) were observed

I have not been able to associate the type of edema with any definite lesion of the heart, as it has appeared during the course of most of the

2 Resnik, William H, and Keefer, Chester S The Significance of Edema of the Face in Myocardial Insufficiency, *J A M A* **85** 1553 (Nov 14) 1925  
3 Cohen, Milton B Edema in Myocardial Insufficiency, Correspondence, *J A M A* **85** 1829 (Dec 5) 1925  
4 Mackenzie, James Diseases of the Heart, ed 3, London, Oxford University Press, 1918, p 307  
5 Miller, R The Medical Diseases of Children, Bristol, John Wright & Sons, 1911, p 374  
6 Crummer, Leroy Clinical Features of Heart Disease, New York, Paul B Hoeber, 1925, p 24

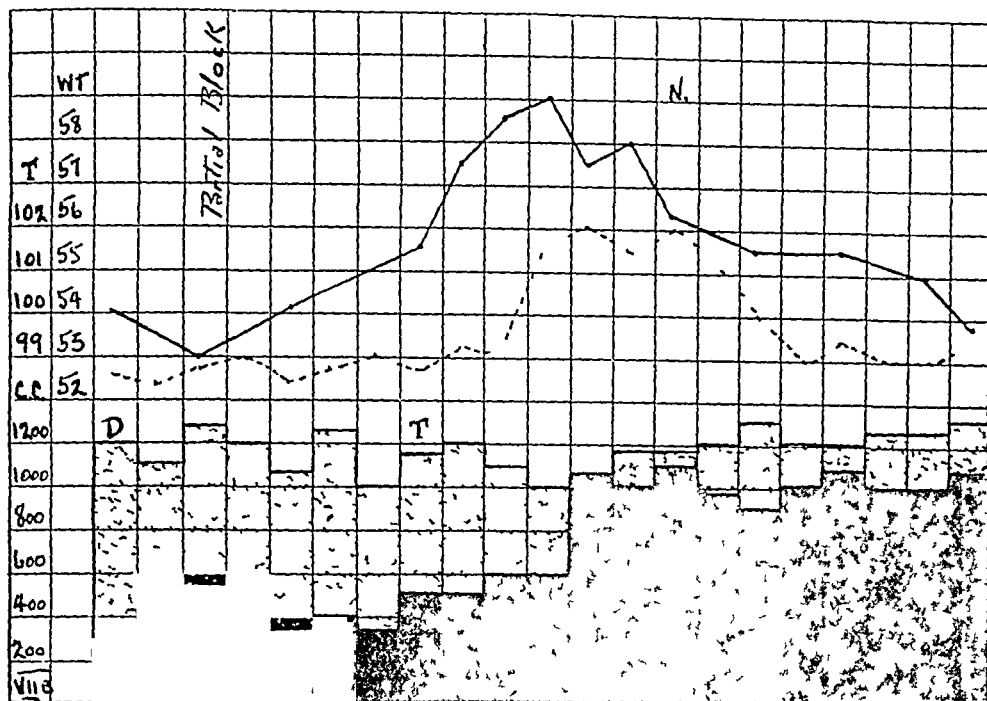


Chart 2—Generalized edema In spite of digitalis (*D*) carried to the point of block, elimination did not occur Following the administration of theobromine sodio-salicylate (*T*) diuresis together with a rise in temperature and toxic symptoms (*N*) appeared

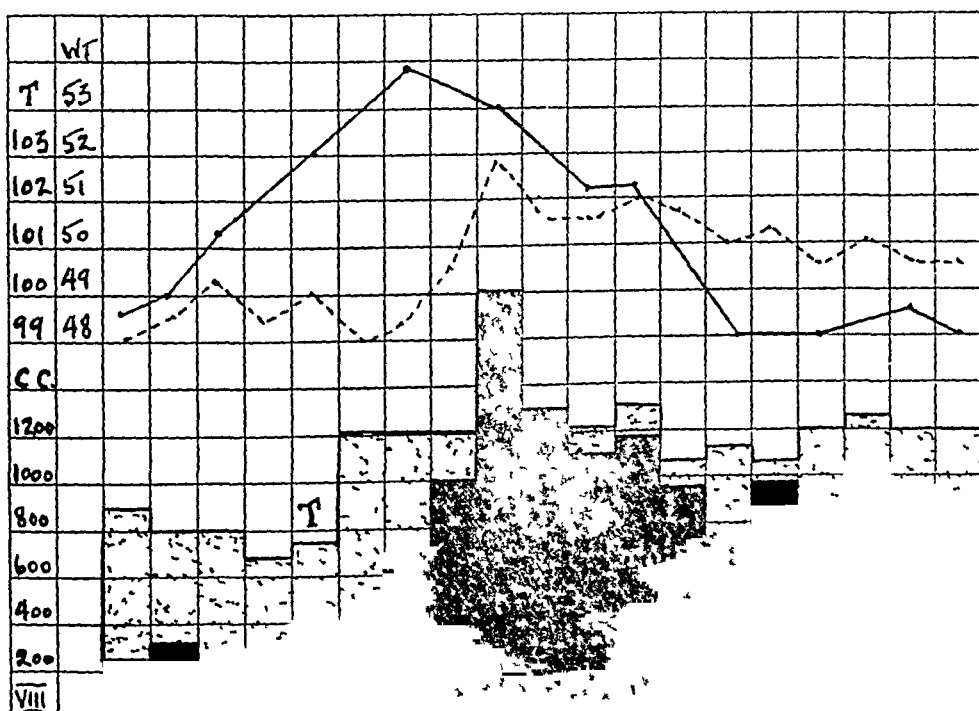


Chart 3—Generalized edema Theobromine sodio-salicylate (*T*) produced elimination with a rise in temperature

clinical types commonly encountered in childhood. There appears, however, to be some definite relationship between generalized type of edema and the recentness of the infectious invasion of the heart. In other words, when the reserve of the chronically diseased heart has been encroached on and failure ensues, a dependent type of edema usually is produced, while in the recently invaded heart, in which one feels there is still active infection, a generalized edema is more likely to occur. In either case, infection is an important factor, for I am convinced that cardiac failure in childhood is generally infectious in origin, though the active process may frequently be extracardiac. It may be possible

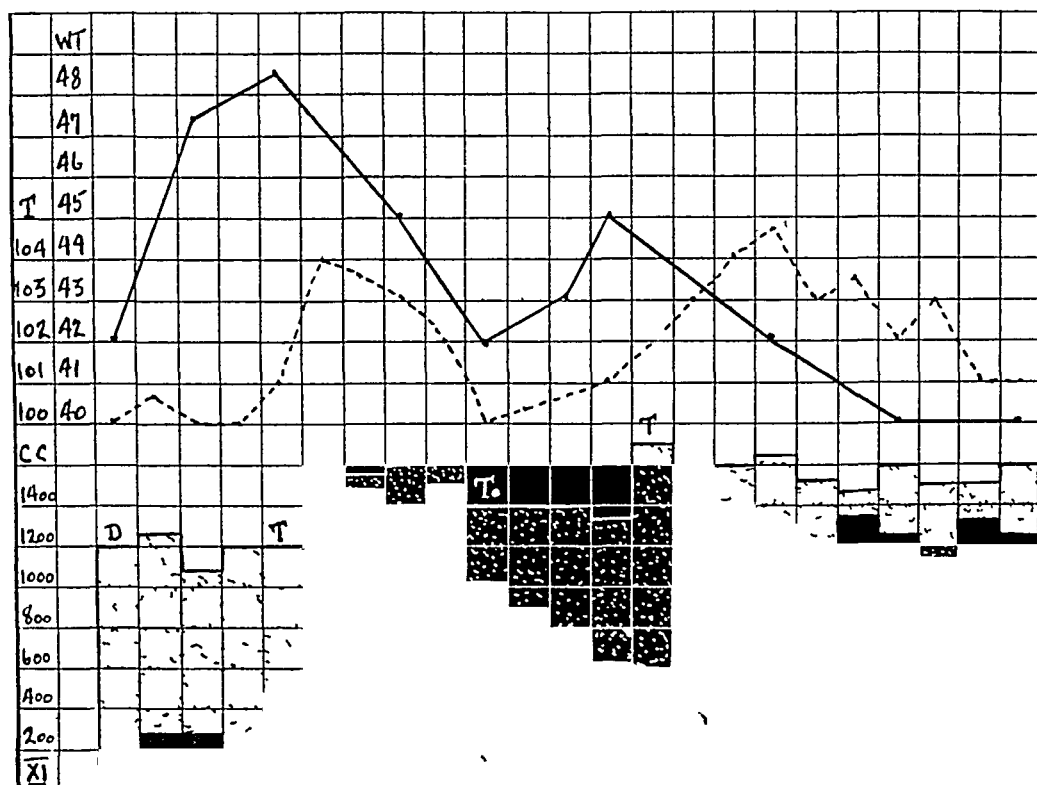


Chart 4—Generalized edema. There was no response with digitalis (*D*). Theobromine sodio-salicylate (*T*) produced elimination with a rise in temperature, when omitted (*To*) edema and weight increased. Elimination was reestablished with theobromine sodio-salicylate (*T*) with toxic symptoms and a rise in temperature.

at some later date, after further observations have been made, to formulate a more definite relationship between the type of lesion of the heart and the type of edema revealed. For the present, my observations lead me to think that it depends rather on the stage of the cardiac involvement, as to whether the infectious process is acute or chronic.

Further convincing evidence that two definite types of edema occur in heart failure in children is presented by the clinical courses of these

attacks It was noted that in the generalized type, following the improvement of the condition of the heart, together with the reabsorption of the edema fluid, increased elimination and subsequent loss of weight, and toxic symptoms occurred For the most part these were mild, consisting of headache, nausea and a rise in temperature On two occasions they were moderately severe It was thought at first that these symptoms were possibly due to the therapeutic measures resorted to in attempting to reestablish the heart and prompt elimination This

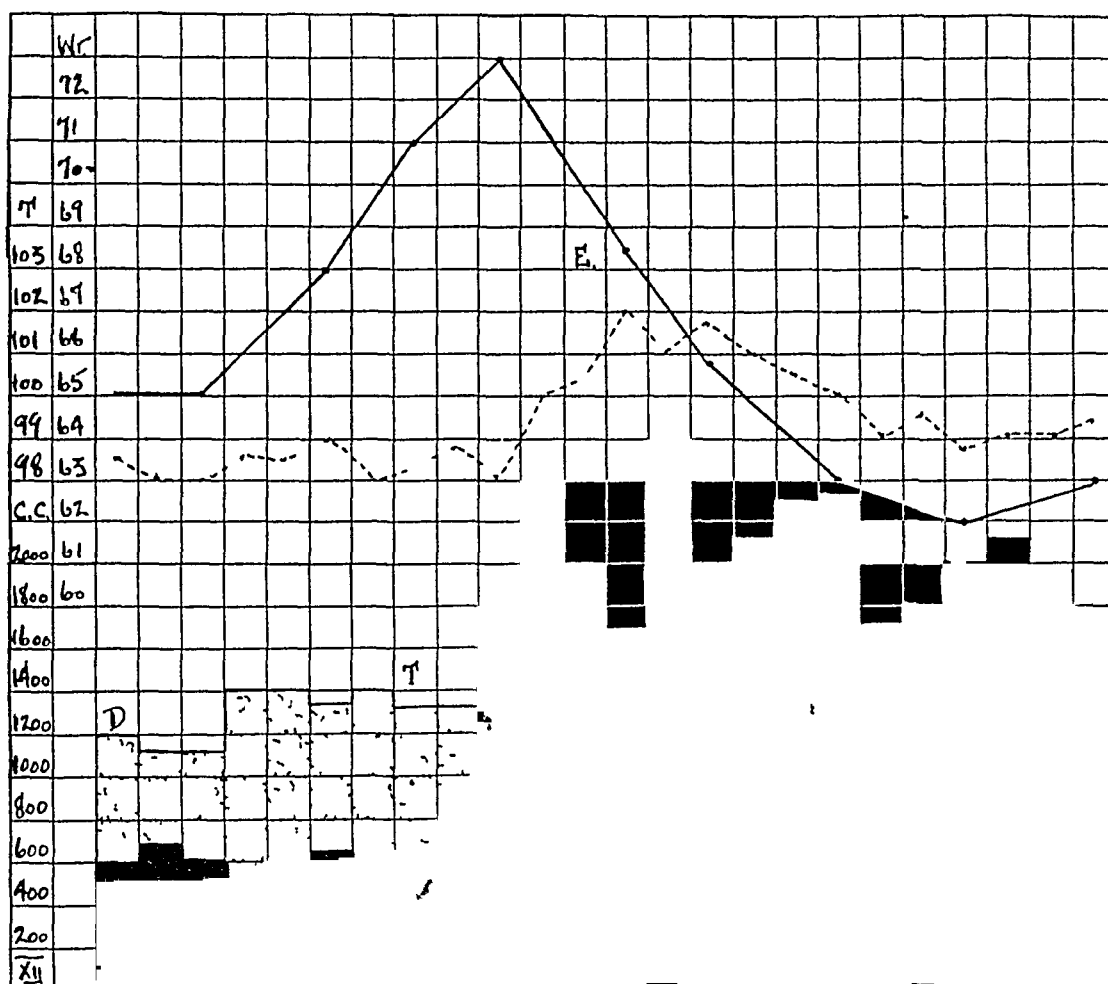


Chart 5—Generalized edema The administration of digitalis (*D*) after a long period did not give results Following the use of theobromine sodio-salicylate (*T*) elimination was established A rise in temperature, toxic symptoms and emesis (*E*) followed

possibility has been disproved by the observation that many other patients underwent the same treatment with equally large doses of the drugs employed and showed neither toxic symptoms nor a rise in temperature The marked elevation of temperature during and following elimination is a convincing observation and is easily demonstrated from charts (charts 1, 2, 3, 4 and 5) If the temperature had been

normal during the edematous stage, a rise was noted with elimination. If the temperature had previously been elevated, it rose higher during diuresis. This toxic phase of the clinical course was a constant observation in the patients with generalized edema, while in those with the dependent type of edema it never occurred (charts 6, 7, 8, 9, 10, 11 and 12).

Furthermore, it was also found that each type responded to different therapeutic measures. Digitalis was, of course, used in most of the cases. In some of the patients seen recently it was used up to the point of digitalization. This was done, not because of definite cardiac

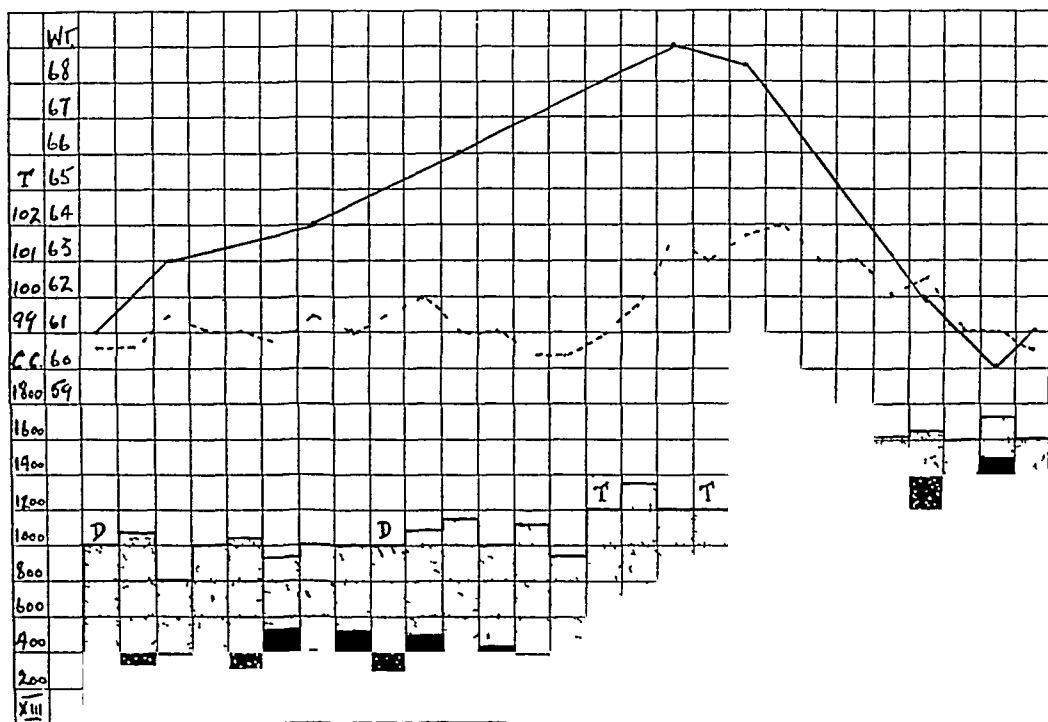


Chart 6—Generalized edema. Repeated use of digitalis (*D*) did not cause elimination. A prompt response occurred with the administration of theobromine sodio-salicylate (*T*). A rise in temperature appeared also.

need, but rather for control purposes to convince myself that digitalis alone was not always the necessary measure to produce diuresis.

It was demonstrated that in the dependent type of edema the use of digitalis was frequently sufficient to cause diuresis and that the addition of the simple diuretics did not hasten or even alter the course. If their combined use had no effect, abdominal paracentesis and merbaphen or organic mercury compound had to be used. Elimination alone, however, in these cases does not appear ever permanently to improve the condition. The mercurial diuretics have given splendid results, but in children the temporary lessening of the cardiac burden as a result

of the enormous elimination produced is rarely sufficient to assist in recovery. I am of the opinion that the reason for this is that the cause of the cardiac failure, infection, is not eliminated, and therefore the process again repeats itself.

In the generalized type of edema digitalis, regardless of the amount prescribed, did not shorten the clinical course of the condition. Theobromine sodio-salicylate, however, acted almost as a specific. Results were obtainable in many of the patients with a generalized type of edema with theobromine sodio-salicylate alone, digitalis not being indicated. This therapeutic response has been so constant that it is now almost a matter of routine, in the ward for patients with cardiac disease, to use theobromine sodio-salicylate in the generalized type of cardiac edemas, while in the dependent type efforts are confined entirely to the

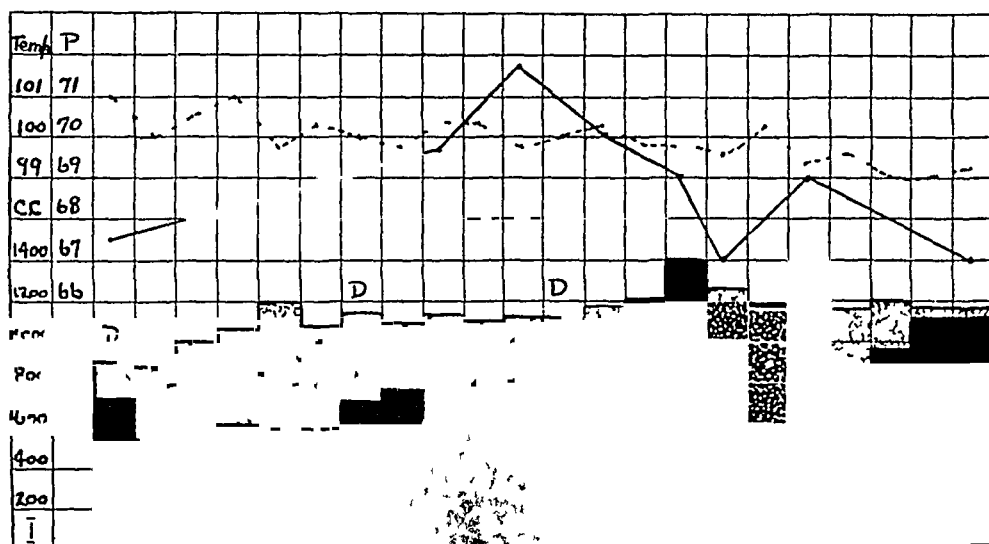


Chart 7—Cardiac edema. The patient responded to increasing doses of digitalis (D). Neither toxic symptoms nor a rise in temperature occurred.

use of digitalis, if no response is noted, the stronger mercurial diuretics are eventually resorted to.

From a prognostic standpoint, the determination of the type of edema present has also been of value. My observations have impressed me with the fact that edema of the dependent type carries with it a grave prognosis. Of the cases reported, five of six patients died. This, of course, is not attributed to the edema per se, but rather to the underlying condition of the heart which, as has been mentioned, is usually chronic.

In the children with generalized edema the immediate prognosis is good. Of the cases reported, only three of ten patients have since died. Ultimately, other cardiac breaks may come with a recurrence of edema of either type, but in the second or even the third attacks of generalized edema the prognosis continues to be better than in the dependent type.



These patients readily respond to treatment and, in spite of the toxic symptoms during the elimination period, their recovery is usually prompt. Other signs of failure, however, may continue after the disappearance of the edema, but these respond to the usual forms of treatment.

## COMMENT

The observation that edema associated with heart failure may be generalized is not entirely new. That it does occur in children, however, as a distinct entity, without a demonstrable pathologic disturbance of the kidneys, responding almost specifically to treatment, producing a definite symptom-complex during diuresis and affording points of prog-

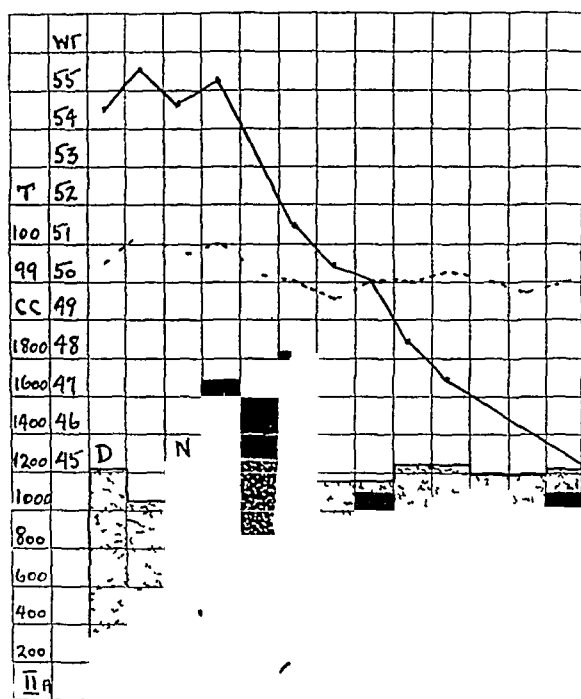


Chart 8—Cardiac edema. There was no response to digitalis (*D*) until merbaphen (*N*) was used. Marked elimination and loss of weight resulted without toxic symptoms.

nostic import, has not been previously emphasized. The fact that aside from the commonly recognized dependent type of edema there does occur also this generalized type in the heart failure of childhood, and that each follows a separate and constant course, justifies the conclusion that different factors are at work in each. I do not presume to attempt to explain the mechanism involved, but certain hypotheses present themselves.

In the cases reported, actual lesions of the kidneys can be excluded. Though varying amounts of albumin were present in many of the patients, this observation occurred as frequently in one group as in the other. Casts were not found regularly in any case. Likewise, the

chemical examinations of the blood in neither group showed enough variation to warrant deductions. There were five patients in whom the nonprotein nitrogen was above normal, two of whom had purely dependent edema, while the other three were among those presenting the generalized type. Twice the uric acid was high, but here again the cases were divided equally between the two groups. In all other respects, the chemical readings on the blood were normal.

That edema of the purely dependent type is primarily mechanical in origin no one can deny. It is sometimes puncturable in these children, yet the intradermal salt solution test of McClure and Aldrich,<sup>7</sup> as demonstrated by Olmsted,<sup>8</sup> in children with cardiac disease shows a decreased absorption time in the lower extremities, indicating some

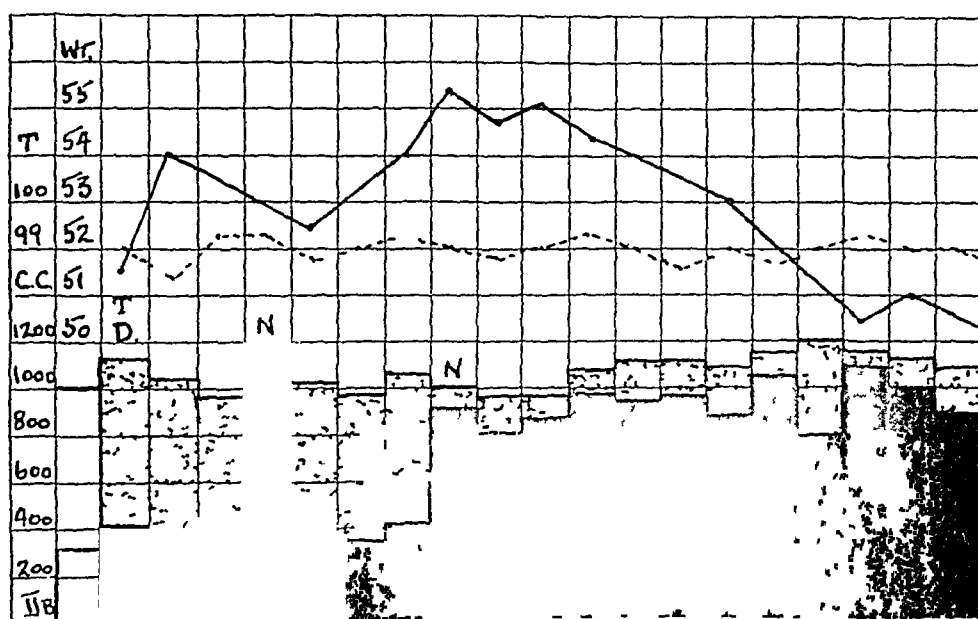


Chart 9—Cardiac edema. There was no response to digitalis (*D*) or theobromine sodium-salicylate (*T*). After two injections of merbaphen (*N*) elimination continued without toxic results.

affinity of the tissues for water. In these conditions the sequence of stasis may occur with subsequent or coincidental change causing an increased demand for water on the part of the tissues, as suggested by Marriott<sup>9</sup> and Fischer.<sup>10</sup>

7 Aldrich, C. A., and McClure, William. The Intradermal Salt Solution Test, *J. A. M. A.* **82** 1425 (May 3) 1924.

8 Olmsted, H. C. Intradermal Salt Solution Test in Cardiac Disease in Children, *Arch. Int. Med.* **37** 281 (Feb.) 1926.

9 Marriott, W. M. Intoxications Associated with Alterations in the Physico-Chemical Equilibria of the Body Cells and Fluids, *Tr. Am. Pediat. Soc.* **35** 205, 1923.

10 Fischer, M. H. Oedema and Nephritis, ed. 3, New York: John Wiley & Sons, 1921, p. 233.



about equal in both the leg and the arm. The time for the leg was a trifle faster, but never by any great margin. In dependent edema there was a difference of from twenty to thirty or more seconds, with the rapid reabsorption always in the leg. Since this test indicates the affinity of the tissues for water, the results would suggest that in generalized edema this affinity is present to an almost equal degree throughout the body. Such a condition of affairs must be explained on a toxic basis. Vaquez<sup>11</sup> and others describes symptoms of a toxic nature following the reabsorption of edema, but did not mention the

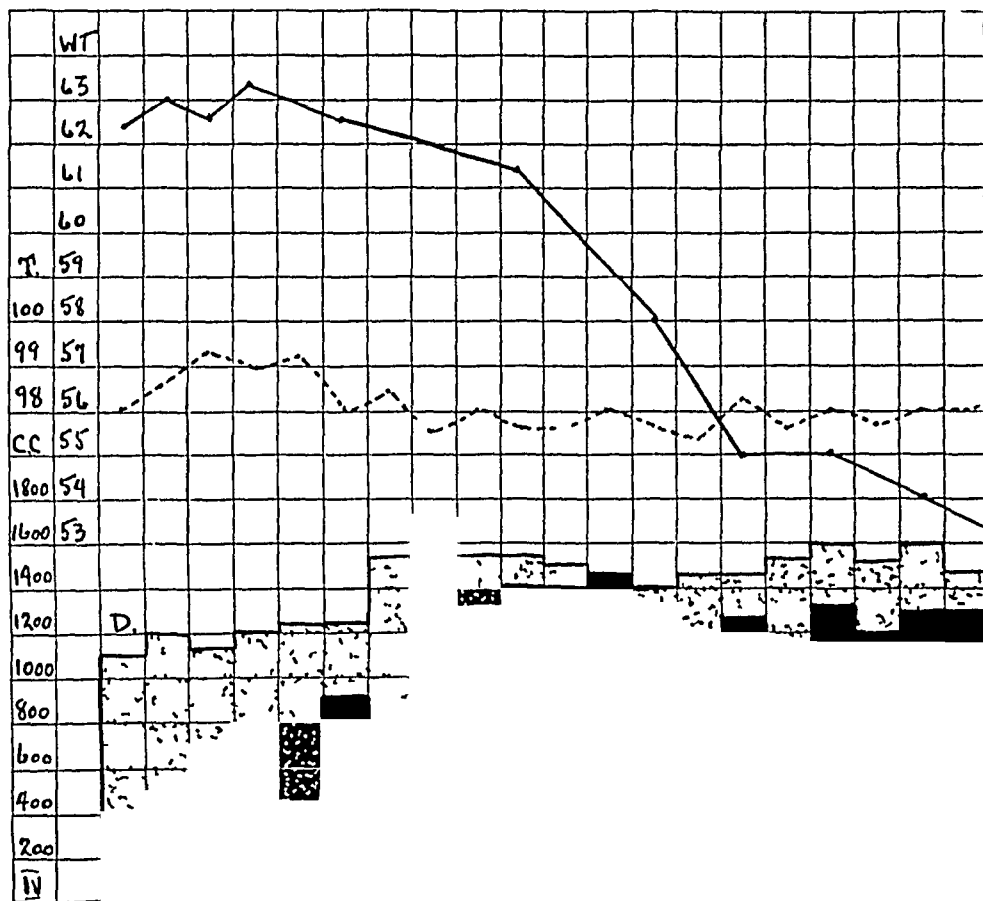


Chart 11—Cardiac edema. Digitalis (D) alone produced elimination

type of edema involved. Vaquez concluded that these symptoms must be contributed to a "sort of conflict within the economy between the organic media and the substances contained in the edematous fluid."

Whatever may be the correct answer to these purely theoretical queries, the fact still remains that in children with heart failure these two types of edema occur, which can be considered definite clinical

11 Vaquez, Henri. Diseases of the Heart, Philadelphia, W. B. Saunders Company, 1924, p. 651.

entities. Also it is true that the recognition of these clinical types of edema is of clinical significance and importance. The therapeutic measures to be instituted are almost specific, depending on the type of edema present, and a correct observation considerably hastens the convalescence of the patient. Likewise, the aid to prognosis is of value. In the cases herein mentioned, dependent edema associated with heart failure in children has always been of serious moment, and only one of the patients has responded permanently to treatment. There have been many others with dependent edema whose course terminated in death before sufficient diuresis occurred so that comparative charts could not be compiled for this study. The prognosis of generalized

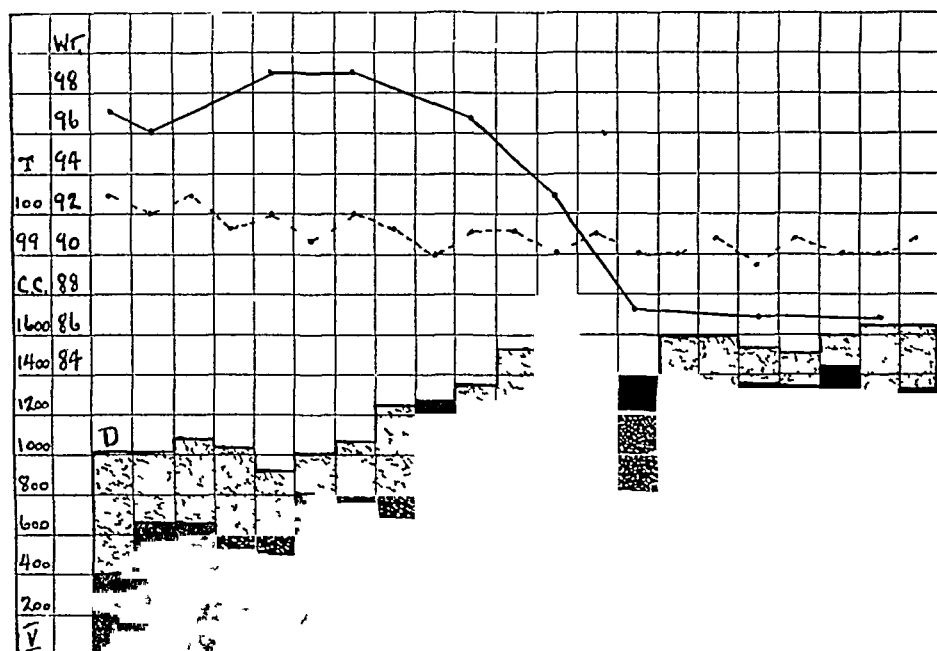


Chart 12—Cardiac edema. Digitalis (D) alone produced elimination

edema is always encouraging, provided there has not been pericardial involvement, which in itself affords, perhaps, the most serious complication in the heart of a child.

#### SUMMARY

1. Edema in the child with cardiac disease manifests itself in two types: the dependent or cardiac type and the generalized or "nephritic" type.

2. Response to treatment has shown a certain specificity which is of clinical value. (a) In the dependent type of edema digitalis is of value, while the addition of the milder diuretics aids little in hastening reabsorption and elimination. If digitalis fails, then the stronger mercurial diuretics are necessary. (b) In the generalized type of edema,

theobromine sodio-salicylate acts almost as a specific and usually without the aid of digitalis

3 In the generalized type, there is a definite clinical picture produced during diuresis which is characterized by toxic symptoms such as headache, nausea and a rise in temperature. In the dependent type of edema these symptoms never occur during diuresis.

4 The type of lesion of the heart seems to influence little the kind of edema produced. It appears, however, that in the children whose history of heart failure is of recent date and whose hearts are, perhaps, still acutely infected, the edema associated with failure is more likely to be generalized. Dependent edema occurs almost exclusively in the patients with more chronic heart disease.

5 The prognosis for the patient with generalized edema is good, at least as to the immediate future, while that of the patient with the dependent type of edema is relatively bad.

6 It is suggested by the clinical observations of two types of edema seen in heart failure in childhood that different factors are at work in each. A few hypotheses have been discussed.

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# PATHOLOGIC CHANGES IN AURICULAR FIBRILLATION AND IN ALLIED ARRHYTHMIAS\*

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From time to time during the past twenty years studies have been made to determine the existence of a specific lesion in auricular fibrillation, auricular flutter and paroxysmal tachycardia. The experiments of Mines and of Garrey demonstrated the possibility of a circus wave of contraction in animal tissues, and those of Lewis showed definitely that circus movement is the mechanism of auricular fibrillation and flutter and possibly of paroxysmal tachycardia. Previous to the time of these experiments, pathologists were prone to consider lesions in or around the sino-auricular and auriculoventricular nodes as of great importance in these arrhythmias, and especially in auricular fibrillation. Recently, little in the way of microscopic study has been done in this field, but the consensus of opinion seems to be that there is no specific pathologic picture. From the standpoint of the new physiology, no visible organic disease is necessary, and the facts that auricular fibrillation and flutter may be paroxysmal and that the former may often be converted to normal sinus rhythm, no matter what the etiologic factor may be, by means of drugs which could not possibly alter structural disability are strong proofs for the nonexistence of a specific organic causative lesion. The present study has been made as an attempt to settle definitely, by microscopic methods, the question of a specific anatomic basis for these arrhythmias.

## REVIEW OF LITERATURE

Most of the investigations of this problem were reported during the years from 1909 to 1915. Schonberg,<sup>1</sup> in 1909, carefully examined eleven hearts with perpetual arrhythmia, and Hedinger,<sup>2</sup> in 1910, added nine cases to these. All of these hearts showed changes in the regions of the mouths of the venae cavae and especially in the vicinity of Wenckebach's bundle. These changes consisted of lymphocytic collections, increase in fibrous connective tissue, or even atrophy and disappearance of the muscle fibers, with connective tissue replacement. In the nerves and ganglions lymphocytic collections or cellular masses con-

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1 Schonberg, S. Ueber Veränderungen im Sinusgebiet des Herzens bei chronischer Arrhythmie, Frankfurt Ztschr f Path 2 153, 1909

2 Hedinger, Ernst. Ueber Herzbefunde bei Arrhythmia perpetua, Frankfurt Ztschr f Path 5 296, 1910

sisting of spindle cells and lymphocytes often occurred. The auriculo-ventricular node was not usually involved. In other hearts without the arrhythmia, these changes usually were not found. Hedinger concluded that auricular fibrillation was probably due to lesions in the region of Wenckebach's bundle and the inferior vena cava.

In 1910, Koch<sup>3</sup> studied three hearts in which fibrillation had occurred. He also found inflammatory changes in the region of the orifices of the venae cavae in all and involvement of the nerves and ganglions in two. There were some changes in the sino-auricular node in all three. In one case, marked interstitial edema in this region and swelling of the muscle fibers were noted. Koch did not come to any definite conclusion regarding the cause of auricular fibrillation from this study, but in a later work he remarked that it is less the inflammatory infiltration of the sino-auricular node than the transcendancy of a new center of auricular impulse and exhaustion of the normal center by over-extension which is most important.

Draper,<sup>4</sup> in 1911, and Cohn,<sup>5</sup> in 1911, each reported the study of a case of auricular fibrillation in which there were severe pathologic changes in the sino-auricular node and other alterations elsewhere in the heart, but without marked lesions of the conduction system. In Cohn's case there was interstitial myocarditis, especially in the right auricle.

Freund,<sup>6</sup> in 1912, found changes such as sclerosis and lymphocytic infiltration in the sino-auricular node in three of five cases of auricular fibrillation. In four of the cases sclerosis of the auriculoventricular bundle occurred, and lymphocytic infiltration in two. In the fifth case there were no changes. Freund assumed that the irregular ventricular activity was due to impairment of conduction through a diseased auriculoventricular bundle, and that the only difference between heart block and auricular fibrillation was the failure of auricular activity in the latter.

Falconer and Dean,<sup>7</sup> in 1911, and Cohn and Lewis,<sup>8</sup> in 1912, each reported a case which showed sufficient destruction of the bundle of His.

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3 Koch, Walter. Zur pathologischen Anatomie der Rhythmusstörungen des Herzens, *Berl klin Wchnschr* **1** 1108, 1910.

4 Draper, G. Pulsus Irregularis Perpetuus with Fibrosis of the Sinus Node, *Heart* **3** 13, 1911.

5 Cohn, A. E. A Case of Bradycardia with Post-Mortem Examination, *Heart* **3** 23, 1911.

6 Freund, H. A. Klinische und pathologisch-anatomische Untersuchungen über Arrhythmia perpetua, *Deutsches Arch f klin Med* **106** 1, 1912.

7 Falconer, A. W., and Dean, George. Observations on a Case of Heart Block Associated with Intermittent Attacks of Auricular Fibrillation, *Heart* **3** 247, 1911.

8 Cohn, A. E., and Lewis, Thomas. Auricular Fibrillation and Complete Heart Block, A Description of a Case of Adams-Stokes' Syndrome, including the Post-Mortem Examination, *Heart* **4** 15, 1912.



to account for the chronic heart block which had existed. In the first case there also had been attacks of auricular fibrillation, and in the latter this arrhythmia had developed. There was no change in the sino-auricular node in the one, but marked sclerosis of the node in the other. There was, however, an increase of fibrous tissue in the right auricle in both instances. A similar case of Angyan,<sup>9</sup> in 1913, with complete auriculoventricular dissociation and subsequent development of auricular fibrillation showed complete division of the bundle of His by fibrous and fatty tissue and severe sclerosis of the sino-auricular node. Falconer and Dean,<sup>10</sup> in 1912, reported another case in which chronic auricular fibrillation had been complicated by occasional attacks of incomplete heart block. In addition to various valvular and muscular lesions there was extensive fibrosis and cellular infiltration of the auriculoventricular node and bundle and cellular infiltration of the sino-auricular node.

In 1912, Price and Mackenzie<sup>11</sup> reported a case of diphtheria with auriculoventricular dissociation and auricular fibrillation in which there was extreme degeneration and cellular infiltration of the cardiac muscle but no changes in the sino-auricular node or conduction system. Hume,<sup>12</sup> in 1913, studied a case of diphtheria with auricular fibrillation and found the sino-auricular node infiltrated with numerous mononuclear cells of the "formative type" and the specific fibers undergoing granular degeneration.

In 1913, Berger<sup>13</sup> reported a study of three cases of auricular fibrillation. In one the sino-auricular node was completely destroyed, and in the other two the specific system was not affected. He considered the fibrillation in the first case due to destruction of the node and in the other two, to dilatation of the right auricle.

Cohn,<sup>14</sup> in 1913, in a study of three cases of auricular fibrillation in horses, found the sino-auricular node and conduction system intact in all.

In 1913, Cohn and Heard<sup>15</sup> found changes in the specific nodes and the bundle of His in one case of auricular fibrillation but doubted any direct connection between the anatomic and clinical observations.

<sup>9</sup> Angyan. Kammerautomatie und Vorhofflimmern, *Virchows Arch f path Anat* **213** 170, 1913.

<sup>10</sup> Falconer, A. W., and Dean, George. Observations on a Case of Auricular Fibrillation with Slow Ventricular Action, *Heart* **4** 87, 1912.

<sup>11</sup> Price, F. W., and Mackenzie, Ivy. Auricular Fibrillation and Heart Block in Diphtheria, *Heart* **3** 233, 1911-1912.

<sup>12</sup> Hume, W. E. A Polygraphic Study of Four Cases of Diphtheria, *Heart* **5** 25, 1913.

<sup>13</sup> Berger. Anatomische Untersuchungen des Herzens bei Pulsus irregularis perpetuus, *Deutsches Arch f klin Med* **112** 287, 1913.

<sup>14</sup> Cohn, A. E. The Post-mortem Examination of Horses' Hearts from Cases of Auricular Fibrillation, *Heart* **4** 221, 1913.

<sup>15</sup> Cohn, A. E., and Heard, J. D. A Case of Auricular Fibrillation, with a Postmortem Examination, *Arch Int Med* **11** 630 (June) 1913.

Sutherland and Coombs,<sup>16</sup> in 1913, in a case of acute rheumatic carditis, discovered the sino-auricular node to be more strongly attacked by focal rheumatic myocarditis than the surrounding auricular muscle, and the conduction system showed diffuse infiltration

In 1914, Romeis<sup>17</sup> reported three cases of auricular fibrillation in which severe sclerosis of the sino-auricular node was shown, but the auriculoventricular conduction system was intact in two

In 1914, Jarisch<sup>18</sup> reported eight cases of auricular fibrillation in only two of which the sino-auricular node was intact. In all of the others there were moderate or severe changes in this node, and in all but two there were lesions in the conduction system. Jarisch concluded that there is, however, no specific pathologic condition in auricular fibrillation. He considered that the arrhythmia was a result of exhaustion of the sino-auricular node, incoordination between the activity of the sino-auricular and auriculoventricular nodes, the disturbing influence of impulse formation in other places and the supremacy of vagus influence when the activity of the sino-auricular node is depressed.

Hochhaus and Dreesen,<sup>19</sup> in 1915, found increase in connective tissue and cellular infiltration of the sino-auricular node in a case of auricular fibrillation, but Thorel,<sup>20</sup> in 1915, could not find pathologic changes in the right auricle or the specific nodes in a heart that he examined.

Wilkinson and Butterfield,<sup>21</sup> in 1915, in a case of paroxysmal heart block and auricular fibrillation, noted collections of small lymphocytes and vascular changes in the auriculoventricular node and bundle and an increase in fibrous tissue in the right auricle but no lesions in the sino-auricular node.

In 1922, Fløystrup<sup>22</sup> studied nine cases of auricular fibrillation and six control cases with special reference to the microscopic changes in the sino-auricular node, the auricles and the nerves and ganglions near the node. In a few of the cases of auricular fibrillation, he found both fatty

16 Sutherland, G. A., and Coombs, C. F. A Case of Acute Rheumatic Carditis and Auricular Fibrillation in a Child, *Heart* **5** 15 1913

17 Romeis, B. Beitrage zur Arrhythmia perpetua. *Deutsches Arch f klin Med* **114** 580, 1914

18 Jarisch Adolf. Zur pathologischen Anatomie des Pulsus irregularis perpetuus, *Deutsches Arch f klin Med* **115** 331 1914

19 Hochhaus and Dreesen. Vorkommen und Bedeutung von anatomischen Veränderungen des Herzmuskels bei Herzschwäche, *Festschr d Akad f prakt med zu Köln*, 1915, p 384

20 Thorel, C. Pathologie der Kreislautorgane des Menschen. I Anatomie des Herzens, *Ergebn d allg Path u path Anat* **17**.90, 1915

21 Wilkinson, K. D., and Butterfield, H. G. Paroxysmal Heart Block with Paroxysmal Auricular Fibrillation, *Heart* **6** 3 1915-1917

22 Fløystrup G. Studies on the Pathogenesis of Auricular Fibrillation. *Acta med Scandinav* **56** 12 1922

infiltration and fibrosis of the sino-auricular node, in one there was lymphocytic infiltration of the node, in a few, only some fatty infiltration of the node. The control cases usually showed similar conditions. After reviewing these cases, together with nineteen from the literature, he concluded that the cause of auricular fibrillation is not to be found in alterations in the sino-auricular node, in changes in the auricular myocardium, in dilatation of the auricles or in anatomic changes in the nerves. He argued that since quinidine caused cessation of the arrhythmia by its depressant effect on muscular activity, the fibrillation might be due to overexcitability of the auricular myocardium due to its working against an absolutely or relatively increased resistance. He believed that nervous influences might be of greatest importance in cases of paroxysmal fibrillation.

Monckeberg,<sup>23</sup> in 1924, after reviewing the literature on the microscopic researches in auricular fibrillation, concluded that the arrhythmia is not dependent on disease of the sino-auricular node or on phenomena of interference between this node and the auriculoventricular node. He believed that the activity of the sino-auricular node not only is not depressed in auricular fibrillation but takes part even in the production of the stimuli leading to the fibrillation. To him Lewis'<sup>24</sup> explanation of the arrhythmia precluded the necessity of anatomic changes either in the specific system or in the myocardium.

In 1925, Frothingham<sup>25</sup> examined the auricles in eleven cases of acute and chronic auricular fibrillation and in twenty-three cases in which death occurred from acute or chronic disease but in which the heart action was regular. He did not find a gross lesion to be constant or essential, nor did he find definite or specific microscopic lesions in the sino-auricular node in cases of auricular fibrillation. He called attention to a certain appearance of the auricular muscle fibers in nine of the eleven cases of auricular fibrillation, and in four of the fifteen controls, which he was unable to decide had any significance for the fibrillation. Throughout the auricles there was edema of the muscle fibers with vacuolization and slight changes in the staining reaction suggestive of degeneration in these cases. In the more advanced form the vacuolization increased, the striations in the fibers disappeared in part and the changes in staining reaction were more marked. The nuclei of the fibers showed little if any change, and the disturbance in the fiber did

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23 Monckeberg, J. G. Herz, in Henke, F. and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, vol. 2, Berlin, Julius Springer, 1924, p. 512.

24 Lewis, Thomas. *The Mechanism and Graphic Registration of the Heart Beat*, ed. 3, London, Shaw & Sons, 1925.

25 Frothingham, C. The Auricles in Cases of Auricular Fibrillation, *Arch Int Med* 36:437 (Sept.) 1925.

not necessarily extend over its length. There was little if any cellular reaction in the supportive connective tissue framework. Marked interstitial edema sometimes occurred, but it also was found in the control cases at times.

In 1928 Condorelli<sup>26</sup> reported an unusual case of auricular fibrillation with nodal rhythm of a frequency of 97. Extensive and highly inflammatory lesions of the subepicardial nerve plexus of the right auricle were present without other important lesions elsewhere in the heart tissue.

The literature contains the reports of only a few cases of auricular flutter in which a careful study of the heart was made. Ritchie<sup>27</sup> in 1914 in a review of cases of auricular flutter recorded the results in six necropsies. In one the auriculoventricular bundle was fibrous. In another there was acute pericarditis implicating the sino-auricular node and the abundant nerve elements in its vicinity. One heart showed diffuse intertarsicular fibrosis in the thin dilated right auricle and slight lymphocytic infiltration in some parts of the conduction bundle. The specific system was normal in a fourth heart and there was slight fibrosis of the muscle. A case of diphtheria presented fatty degeneration of auricles and ventricles and pronounced interstitial myocarditis of the ventricles; the auriculoventricular node and bundle were healthy. Another case of diphtheria showed infiltration of the sino-auricular node with mononuclear cells of 'formative type' and engorged capillaries and hemorrhages; the muscle fibers of the node were in a state of granular degeneration. Sutherland,<sup>28</sup> in 1914 and Neuhoef<sup>29</sup> in 1915 each reported a case without any specific changes.

The literature on studies of cases of paroxysmal tachycardia is also meager. Vaquez<sup>30</sup> in 1909 and Cade and Rebattu<sup>31</sup> in 1911 each recorded a case with changes in the bundle of His. Falconer and Duncan<sup>32</sup> in 1912 a case of 'syphilitic myocarditis' with endarteritis in which the sino-auricular node and conduction system were affected.

26 Condorelli Luigi. Sull'importanza delle lesioni infiammatorie del plesso sottoepicardico dell'orecchietta destra nella patogenesi di alcune turbe del ritmo cardiaco. *Riforma med.* **44** 613 1928.

27 Ritchie W. T. *Auricular Flutter*. New York: Paul B. Hoeber, 1914.

28 Sutherland G. A. Auricular Flutter in Acute Rheumatic Carditis, *Proc. Roy. Soc. Med.* **7**:133 1914.

29 Neuhoef Selian. Auricular Flutter Accompanying Acute Endopericarditis, *M. Rec.* **88** 995 1915.

30 Vaquez H. Pathogenie de la tachycardie paroxystique. *Arch. d. mal. du coeur* **2** 609 1909.

31 Cade A. and Rebattu I. Tachycardie paroxystique et lesions du faisceau de His. *Bull. et mem. Soc. med. d. hop. de Paris* **31**:476 1911.

32 Falconer, A. W. and Duncan G. M. Observations on a Case of Paroxysmal Tachycardia of Auricular Type. *Heart* **3** 133 1912.

A case reported by Falconer and Dean, in 1912, revealed rheumatic nodules with infiltration of the membranous septum and middle third of the crus communis in a case of this arrhythmia. In 1914, Butterfield and Hunt<sup>33</sup> reported a case in which there were changes in the wall of the auricle and sino-auricular node. Monckeberg concluded that these changes were not consistent enough to account for the arrhythmia, since analogous observations have been made in the specific muscle system without clinical evidence of either a shunting out of the sino-auricular node or an increased automatic activity of the auriculoventricular node, which the observations in these cases were supposed to indicate.

#### ANALYSIS OF CASES

A series of 145 cases of auricular fibrillation, seven cases of auricular flutter and two cases of paroxysmal tachycardia, all with necropsies, was studied. The cases included practically all of the patients with these arrhythmias on whom necropsies were performed at The Mayo Clinic within the last few years, they were not a selected group. One begins to realize that the subject of cardiac disease cannot be discussed apart from the clinical course, because so few specific lesions are demonstrated. This entire series was investigated, therefore, to determine the clinicopathologic basis of the arrhythmia, and from the three groups of arrhythmias, hearts were selected for microscopic study with reference to their classification on such a basis. In all but a few of the cases the arrhythmia had been confirmed by the electrocardiogram, in the few exceptions, there was no reasonable doubt regarding the type of arrhythmia. As far as consideration of the clinical investigation combined with the necropsy examination would permit, the grouping of the cases was determined as follows:

*Auricular Fibrillation (145 Cases)*—Endocarditis (Twenty-Eight Cases). In eleven of these cases there was a definite history of rheumatic fever. The lesions were distributed as follows:

There were fourteen cases of mitral stenosis. In thirteen of these the fibrillation was apparently chronic, in one, it was a terminal event. There were six men and eight women. The youngest patient was 28 years of age, the oldest 72, and the average age was 43.

There were nine cases of combined mitral and aortic endocarditis, in all of which the fibrillation was assumed to be chronic. There were four men and five women. The youngest patient was 31 years of age, the oldest 54, and the average age was 42.

There were three cases of aortic stenosis with calcification of the aortic valve. All were apparently cases of chronic fibrillation, and all patients were men. Two were 62 years of age and one was 64.

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33 Butterfield, H. G., and Hunt, G. H. Observations on Paroxysmal Tachycardia, *Quart. J. Med.* 7: 209, 1914.

There were two cases of subacute mitral endocarditis. One was rheumatic, the other bacterial in origin. The patients were both men, 21 years of age, who had chronic fibrillation. Most of the hearts in this group showed moderate hypertrophy, in a few it was extreme.

**Exophthalmic Goiter (Thirty-Six Cases)** The fibrillation was terminal in one case and presumably chronic in the others. There were eleven men and twenty-five women. The youngest patient was 26 years of age, the oldest 68, and the average age was 45. In general, these hearts were only mildly or moderately hypertrophied.

**Adenomatous Goiter with Hyperthyroidism (Twenty-Seven Cases)** In three of these, the fibrillation was practically terminal, occurring for only a few days before death, in the others it was supposedly chronic. The diagnosis in one of these cases was questionable so far as the etiology of the cardiac condition was concerned, because the heart was so hugely hypertrophied (weight 848 Gm). As a rule, these hearts were only moderately hypertrophied. Five of the patients were men and twenty-two were women. The youngest was 47 years of age, the oldest 79, and the average age was 59. These patients were, therefore, considerably older than those with exophthalmic goiter.

**Hypertension (Eleven Cases)** In these eleven cases, hypertension was without doubt the cause of the cardiac failure. In three other cases, hypertension was assumed to be the cause of the cardiac condition because of the great hypertrophy and the absence of any other etiologic factor, but at the time of examination the blood pressures were normal. Of the eleven reasonably certain cases there were six men and five women. The youngest patient was 42 years of age, the oldest 70, and the average age was 56. The age incidence, therefore, was similar to that of the patients with adenomatous goiter. Of the three patients whose cardiac condition presumably was caused by hypertension, two were men and one was a woman, the ages were 54, 63 and 61, respectively. In all, the fibrillation apparently was chronic. As a rule, these hearts showed little coronary sclerosis, but all were considerably hypertrophied.

**Coronary Sclerosis (Four Cases)** There were three men and one woman whose ages were 81, 70, 76 and 72, respectively. Three of these hearts were moderately hypertrophied, and the patients also had hypertension. The other heart presumably was of normal size, but the patient had hypertension. These were all supposedly cases of chronic fibrillation.

**Chronic Adhesive Pericarditis (Two Cases)** These were presumably of rheumatic origin. One patient was a man, aged 57, the other a woman, aged 70. One heart weighed 675 Gm, the other 495 Gm. In both cases, the fibrillation was chronic.

**Syphilis (One Case)** This patient was a woman, aged 35, with syphilitic aortitis and aortic endocarditis. The fibrillation apparently was chronic.

**Combined Conditions (Twelve Cases)** In four cases both adenomatous goiter with hyperthyroidism and hypertension occurred. In three cases both hypertension and coronary sclerosis were present, and because of the degree of hypertrophy the hypertension was assumed to be the primary factor. In two cases the patients had both hypertension and endocarditis. In one case there was adenomatous goiter with hyperthyroidism and chronic adhesive pericarditis, in another, exophthalmic goiter and hypertension, in a third, exophthalmic goiter and coronary sclerosis. In the last, the fibrillation was terminal, but in all the others it presumably was chronic.

**Absence of Any Related Disease (Thirteen Cases)** In these cases the fibrillation was supposedly chronic but an etiologic factor could not be deduced, and the hearts were, as a rule, slightly hypertrophied. There was a history of rheumatic fever in one case. Nine patients were men and four women. The youngest patient was 40 years of age, the oldest 75, and the average age was 54.

**Terminal Auricular Fibrillation (Eleven Cases)** In most of these cases death followed a major operation, and the fibrillation existed for only a few days before death. The hearts were not appreciably enlarged. There were eight men and three women. The youngest was 29 years of age, the oldest 88, and the average age was 64.

**Auricular Flutter**—There were seven cases of auricular flutter. Mitral stenosis existed in one case, adenomatous goiter with hyperthyroidism in one, hypertension in one, and adenomatous goiter with hyperthyroidism and hypertension in one. In two cases a related disease could not be determined, and in one case the patient had an abscess of the lung and cirrhosis of the liver. In one case the flutter had occurred paroxysmally for a year, and in the others it was continuous.

**Paroxysmal Tachycardia**—There were only two cases of this arrhythmia. One patient was a man, aged 78, who died from pyelonephritis and bronchopneumonia four days after excision by cautery of an epithelioma of the base of the bladder. He had had paroxysmal tachycardia for twenty years. The heart weighed 465 Gm and was apparently normal except for one terminal vegetation on the mitral valve. The other patient was a woman, aged 27, whose myocardium was the seat of extensive fibrosis. This was such an unusual case that it will be used as the basis of a separate report.

#### MICROSCOPIC CHANGES

Twenty-nine of these hearts were selected for special histologic examination. Twenty-six were from cases of auricular fibrillation. Of

these, there were eight cases of endocarditis, six of goiter, six of hypertension, two of coronary sclerosis, one case of chronic adhesive pericarditis, one of syphilis and two cases of terminal auricular fibrillation without assignable explanation. Of the other three, there were two cases of auricular flutter and one case of paroxysmal tachycardia. As controls, thirty-five supposedly normal hearts also were studied.

The following routine method of study was adopted. A block of tissue about 2.5 by 1 cm., was taken longitudinally along the edge of the crista terminalis just below the orifice of the superior vena cava. A thread was tied through the end nearest the vena cava and the sections were cut transversely from this end at intervals of 1 mm. This block contained the sino-auricular node. A second block of tissue was excised from the septum of the heart, including part of the interauricular, auriculoventricular and interventricular septum. This block contained the auriculoventricular node and bundle and the first portions of the right and left bundle branches. It was divided into two equal pieces by a vertical incision, and a thread was sewed into the right end of each portion. Sections were taken for microscopic study at intervals of 1 mm. transversely through the two pieces, the ends through which the thread was sewed were used as the tops of the blocks. In this way, a series of sections was made transversely through the auriculoventricular node and bundle and obliquely through the bundle branches.

Two other blocks were removed from the interventricular septum, one on each side, transversely through the regions containing the main right and left bundle branches. These were cut transversely, so that the Purkinje fibers of the bundle branches were seen in cross-section.

In addition, other blocks of tissue were removed from various parts of the heart, one from the wall of the right auricle posteriorly near the right ventricle, one from the left auricle posteriorly near the left ventricle, one from the wall of the right ventricle posteriorly near its middle and one from the left ventricle posteriorly near its base.

All of the blocks of tissue were fixed in a 10 per cent solution of formaldehyde and embedded in celloidin. The microscopic sections were cut 8 microns thick, all were stained with van Gieson's picrofuchsin stain and many with hematoxylin and eosin. In eight supposedly normal hearts and in thirteen of the hearts showing pathologic changes sections of the right auricle in the region of the sino-auricular node containing nerve cells or ganglions, were stained with thionin.

Also frozen sections of the interauricular septum and the left ventricle of all of the hearts were stained with schiälach R. to determine the microscopically visible fat content of the muscle fibers.

*Normal Hearts (Controls)*—The thirty-five supposedly normal hearts were studied in a similar manner especially with reference to the histology and anatomy of the sino-auricular node, conduction system and auricles. The histologic and anatomic structure of the sino-auricular node and conduction system, as described by Keith, His, Tawara, de Witt and others, was confirmed. The sino-auricular node (Keith-Flack) was found to be a relatively long, flat bundle of interlacing, thin fibers in a groundwork of connective tissue, situated subepicardially, just below the mouth of the superior vena cava with its longitudinal axis in the sulcus terminalis. Its cross-section is fusiform or roughly triangular.



laid in shape and down its middle runs the fairly large artery of the node (fig 1). There are also a number of arterioles in its substance, nerves and nerve ganglions are found subepicardially in its vicinity, and often nerves are seen at its edge. In only two instances of all hearts examined, however, was a definite nerve cell seen in the substance of the node. Stained with van Gieson's picrofuchsin, the node is easily identified by its compactness, red color due to the large amount of connective tissue, and the centrally placed artery. In good sections, the cross-striations of

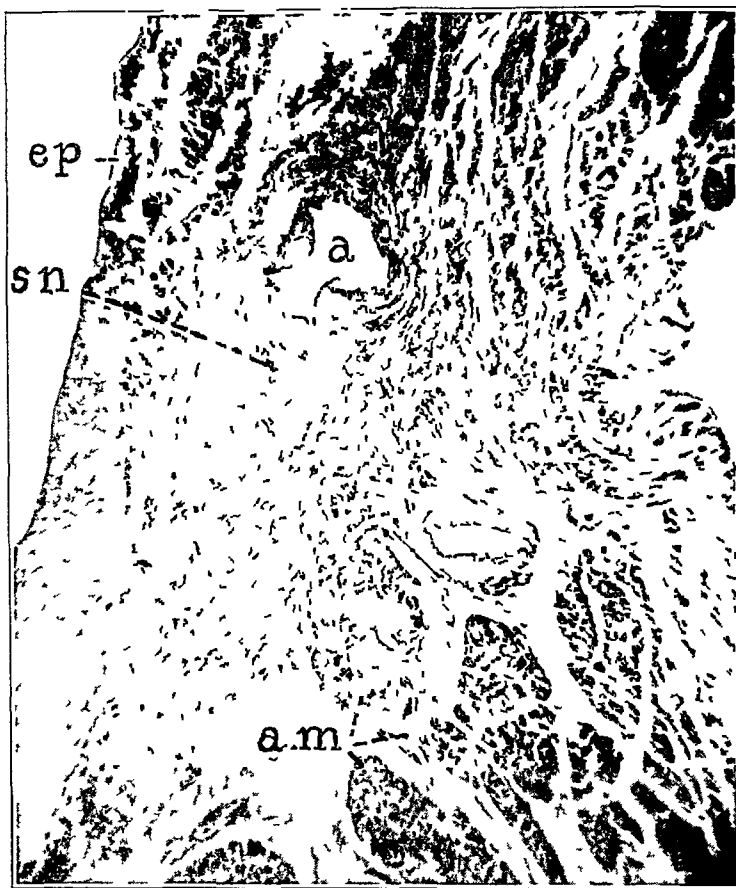


Fig 1—Cross-section of the sino-auricular node, *sn* ( $\times 40$ ) *ep*, epicardium, *a*, artery of the node, *a.m.*, auricular muscle

the individual parenchymatous fibers may be seen. In many cases, however, the detail of the individual fibers cannot be ascertained. Also the amount of connective tissue normally present varies within certain limits. The auricular muscle fibers of the crista terminalis often lie close to the node, and occasionally muscle fibers are seen running along its edge. Adipose connective tissue separates the node from the epicardium. The auriculoventricular node (Tawara) lies close to the right side of the posterior portion of the central fibrous body, that is, in the right auricle a short distance anterior to the orifice of the coronary sinus and just

above the attachment of the medial or septal cusp of the tricuspid valve. A relatively large artery lies in its substance (fig 2). This node is not so compact as the sino-auricular node and contains somewhat less connective tissue. It is flattened out against the central fibrous body, and at its edges the fibers are looser and pass down some distance toward the base of the tricuspid valve. Its fibers are slightly thicker than those of the sino-auricular node, and the cross-striations are more frequently visible. The fibers are arranged in whorls. The artery of this node finally leaves it and passes through the central fibrous body and down into the musculature of the ventricular septum. The node also invades

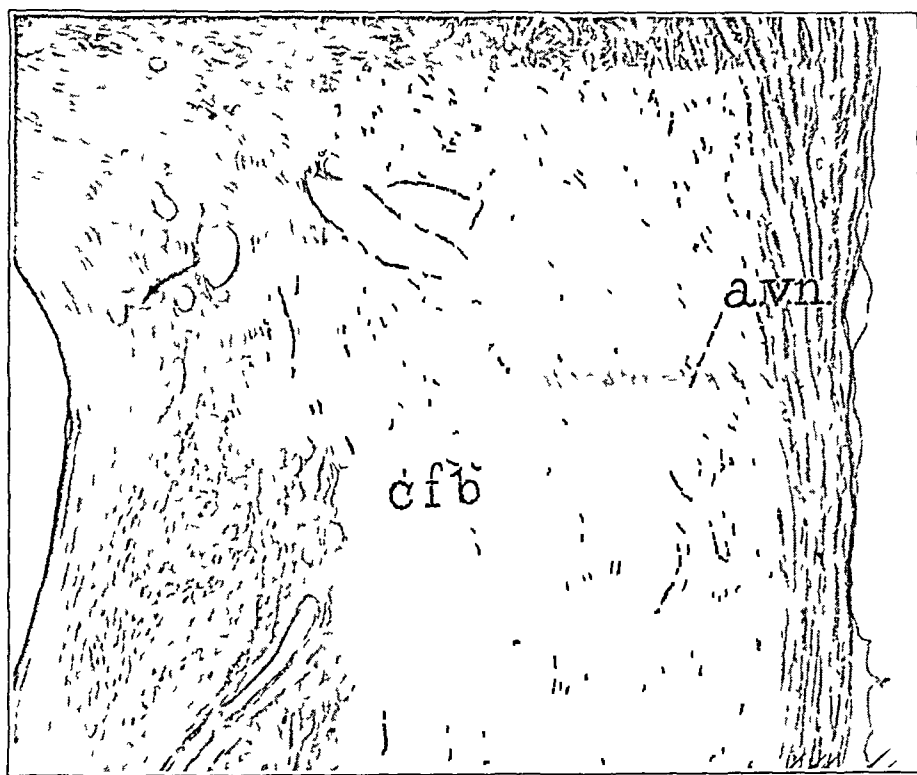


Fig 2—The auriculoventricular node, *avn*, in cross-section, lying against the central fibrous body, *cfb* ( $\times 20$ ). The artery to the node has divided into two branches.

the central fibrous body and merges into the auriculoventricular bundle (Kent, His), which runs obliquely downward in the substance of the central fibrous body and membranous septum at the base of these structures and is separated by a little of the fibrous tissue from the interventricular muscular septum (figs 3 and 4). The fibers are larger than those of the auriculoventricular node and run in parallel bundles. They resemble more the ventricular muscle fibers but do not contain so much myoplasm. The connective tissue framework is delicate, and there is no main artery but a number of arterioles and venules. On cross-section the bundle is roughly triangular, with blunt corners, and the apex

is toward the auricular portion of the heart. Often a fair amount of adipose connective tissue is present. The bundle runs for about from 1 to 1.2 cm. and divides into its right and left branches (fig. 5). The right branch appears to be a continuation of the bundle and passes downward beneath the juncture of the medial and anterior cusps of the tricuspid valve as a white, threadlike or nerve-like process a short distance beneath the endocardium and not distinctly separated from the surrounding heart muscle (figs. 6 and 7). This branch is often difficult to recog-



Fig. 3—The beginning of the bundle of His, *a.v.b.*, in cross-section, as it lies in the edge of the membranous portion of the interventricular septum, *m.s.* ( $\times 20$ )

nize microscopically in the human heart, in fact, I have had more success in gross dissections than in the histologic examination of this branch. The fibers closely resemble the muscle fibers. The right branch passes directly along the trabeculum, which corresponds to the moderator band of the calf heart, to the anterior papillary muscle of the right ventricle. In the cross-sections of the auriculoventricular bundle its origin is often difficult to recognize unless serial sections are made, because it is so small and is cut obliquely in the routine method employed. The left branch is given off at the same point, but it flattens out immediately under the

endocardium of the left ventricle just below the aorta, so in the method employed in this study it is always seen, and is present in all of the sections beyond the point where the branch begins (fig 8) The part of the main bundle from which the two branches have their origin is known as the crux communis and is triangular on cross-section, the two inferior angles representing the points of origin of the bundles The origin of the right branch, when seen, passes out superficially through the ventricular muscle, but the origin of the left is even closer to the

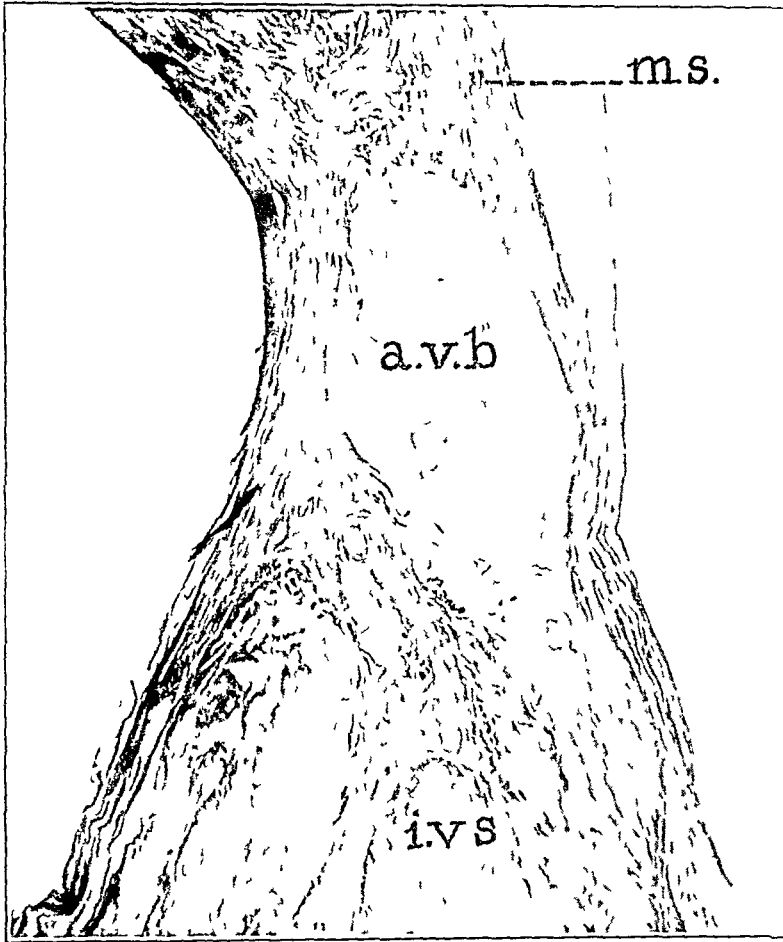


Fig 4—The bundle of His, *a.v.b.*, in cross-section farther along than in figure 3, lying in the membranous portion of the interventricular septum, *m.s.* ( $\times 20$ ), *i.v.s.* muscular portion of interventricular septum

endocardium, the Purkinje fibers are directly beneath the endocardium and usually are distinctly separated from the heart muscle The Purkinje fibers are broader and paler than the muscle fibers and anastomose somewhat less profusely (fig 9) The cross-striations are usually not so distinctly seen as in the ventricular muscle, and the myofibrils are more prominent On cross-section the Purkinje fibers are larger and paler, but are similar to the muscle fibers (fig 10)

The auricular muscle fibers are more wavy, less compact and less anastomotic than the ventricular muscle fibers. These fibers are also usually paler, their myofibrils (the longitudinal lines) are often prominent, the cross-striations may be faint, are sometimes invisible, and often when seen are broken and more prominent at the edge of the fibers. The nuclei are often distorted. The auricles contain considerable subepicardial adipose connective tissue, and in fixation apparently there is more shrinkage and distortion of the sections of the auricle on this

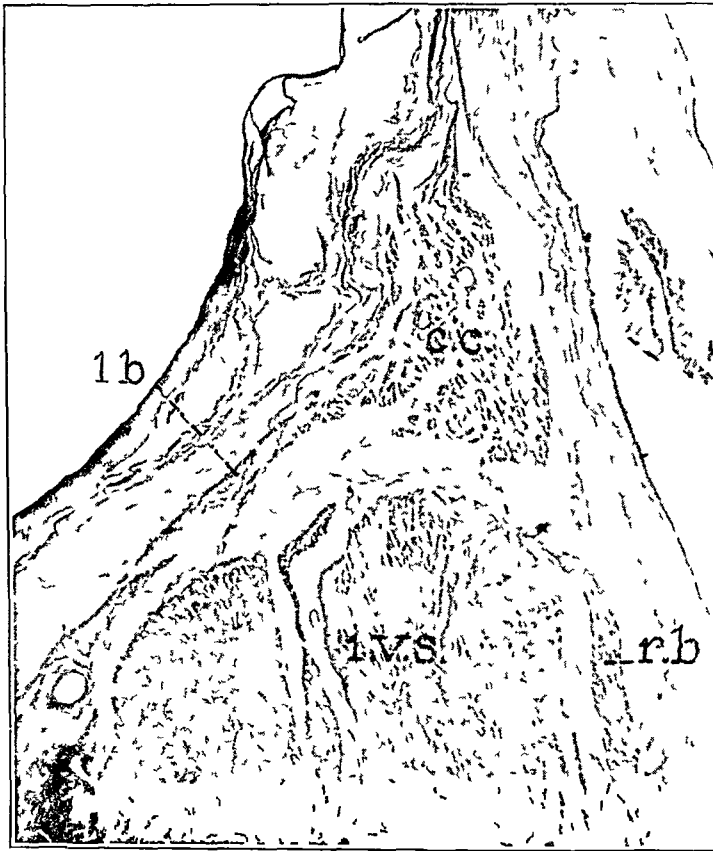


Fig 5—The crux communis, *cc*, in cross-section, with the origin of the left bundle branch, *lb*, and the right bundle branch, *rb* ( $\times 20$ )

account. The epicardium itself is usually thin. The endocardium of the auricles is thick. Adipose connective tissue is not present between the muscle fibers and the endocardium. Often there are a few small lymphocytes in the epicardium. Often the auricular muscle fibers appear to be swollen, in which case they are pale and may contain a large central space apparently devoid of cytoplasm in which the nucleus lies. Frothingham called attention to this and noted that such appearances were also present in some normal hearts. This is undoubtedly true and these phenomena can, therefore, be exonerated as playing a role in the mechanism of arrhythmia.

The histology of the ventricles is better known because routine sections from them are more frequently studied. The sections are always more satisfactory than those of the auricles, perhaps because one presupposes that the sections of the auricle should appear like those of the ventricle. The muscle fibers are darker and more compact, with indistinct myofibrils, but usually there are sharp and regular cross-striations when viewed with subdued light. The nuclei usually are not distorted. The endocardium of the ventricles is rather thin, as opposed to the thick

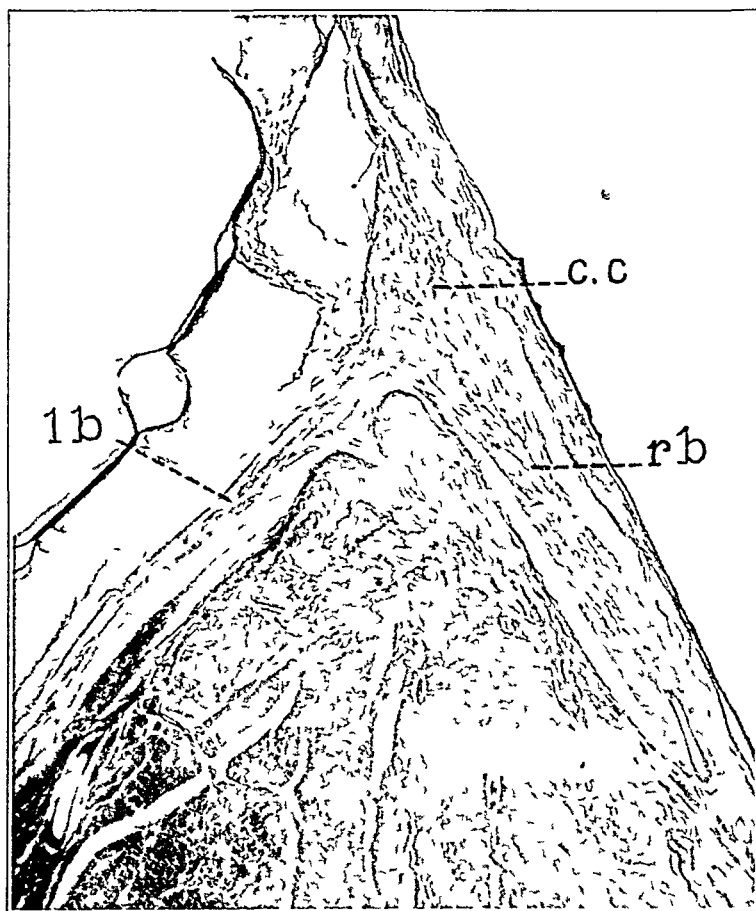


Fig 6—A little farther along than figure 5, showing the origins of the bundle branches more clearly ( $\times 20$ )

endocardium of the auricles. The individual Purkinje fibers cannot usually be recognized.

*Endocarditis*—The group of hearts in which fibrillation occurred in life comprises eight cases of endocarditis and one case of adhesive pericarditis, the latter is considered in this group because of the supposedly similar etiology. There were three cases of mitral stenosis, one case of aortic stenosis with slight involvement of the mitral valve, three cases of combined mitral and aortic stenosis, one case of subacute rheumatic mitral endocarditis and the one case of chronic adhesive pericarditis.

Four patients were men and four women. All were less than 46 years of age except the patient with aortic stenosis who was a man, 54, with calcification of the aortic valve and the patient with chronic adhesive pericarditis who was a man, aged 57. Six patients died of cardiac decompensation directly, one of cerebral embolism complicating decompensation and one of mesenteric thrombosis. The duration of the auricular fibrillation could not be ascertained definitely in any case. This group, as a whole, showed more definite lesions than any of the other

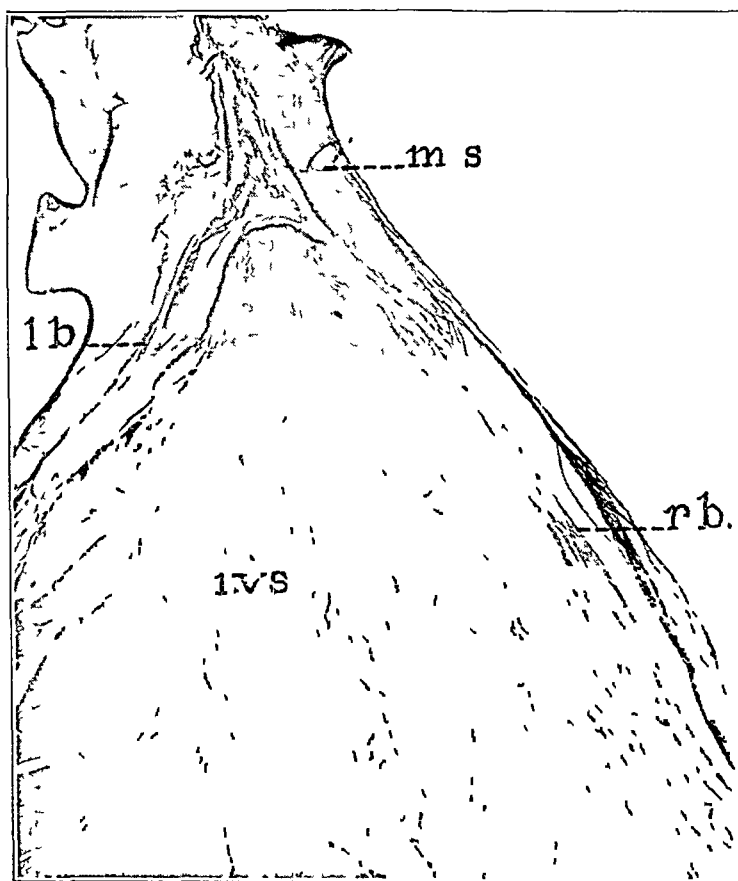


Fig 7—A short distance farther along than figure 6, showing that the bundle of His divides into the two bundle branches, *lb* and *rb* ( $\times 20$ )

groups. In the sino-auricular node the only features of note were an apparent slight increase in connective tissue in one case and a moderate increase in another. In four there were small foci of connective tissue. In one case there were a few small lymphocytes scattered through the node, and in another some small foci of lymphocytes. In one case the nodal fibers were separated more than usual, in one they were less interlacing and in another there appeared to be a diminution in the number of fibers. The detail of the individual fibers was not good in four cases. There was congestion of the node in one instance. The epicardium in

the region of the node contained small lymphocytes in four cases, in two they were few in number, in another they were scattered throughout, and in the fourth they were numerous and collected mainly about blood vessels. Aschoff-like bodies were present in the epicardium and also in the myocardium of the right auricle in only one case, that of a young man, aged 21, with subacute mitral endocarditis whose cardiac symptoms were of nine months' duration, although he had had rheumatic fever nine years before. The epicardium was thickened in one case,

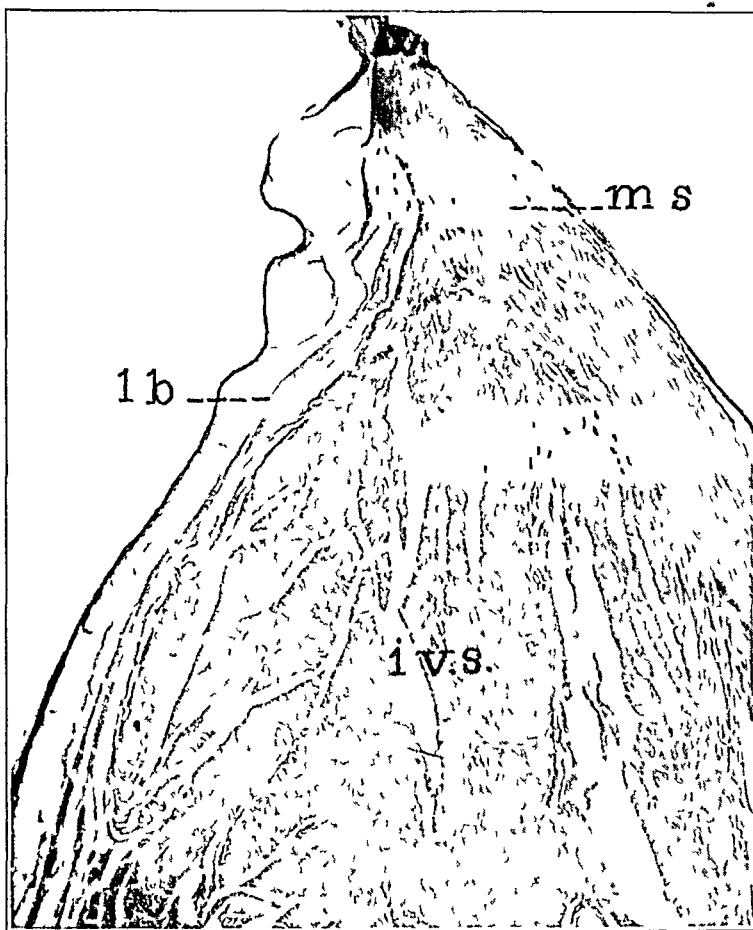


Fig 8—A short distance farther along than figure 7. The right bundle branch is no longer seen, but the left bundle branch, *lb*, being broad and flat, is still present in the section ( $\times 20$ )

and epicardial adhesions occurred in the case of adhesive pericarditis. In three cases there were small lymphocytes in the subepicardial connective tissue, but they were present in large numbers in only one case. Subepicardial hemorrhages were noted in two cases. The muscle fibers of the heart were universally swollen in the region of the node in two cases, and swollen in places in one case. The cross-striations of the muscle fibers were not seen in three cases. The auricular muscle fibers in the other sections of the right auricle were swollen universally in one



case and irregularly in two cases. Cross-situations were practically absent in four cases and present only here and there in another case. The myofibrils were prominent in seven cases.

In one case the auriculoventricular node contained some small lymphocytes together with a few scattered polymorphonuclear leukocytes. The artery of one of the nodes was thickened but was not fibrotic. The auriculoventricular bundle showed shrinkage of its fibers in one instance. Small lymphocytes were scattered throughout the auriculo-

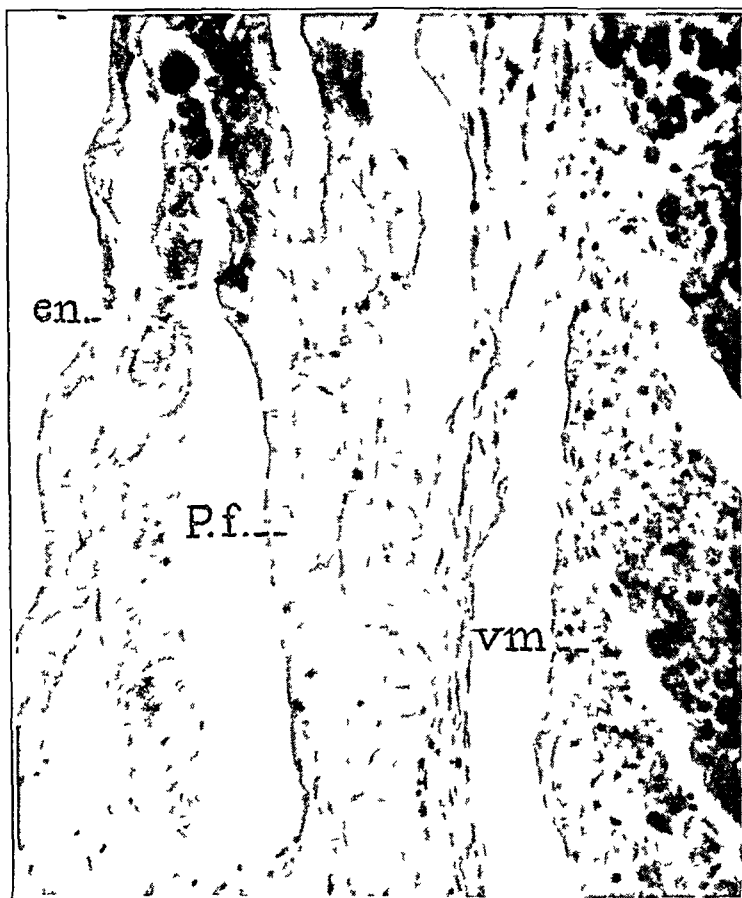


Fig 9—The posterior limb of the left bundle branch, showing the Purkinje fibers, *P.f.*, in longitudinal section beneath the endocardium, *en.*, and the ventricular muscle fibers, *vm.*, in cross-section ( $\times 150$ )

ventricular bundle in one case, and Aschoff-like bodies were in the bundle in the case of subacute endocarditis. In none of the cases did the bundle branches show any features of note, and the right branch was identified in only three cases.

Sections of the left auricles showed even less frequent lesions, which were unimportant and were not of sufficient interest to enumerate. The same general characteristics of the muscle fibers prevailed as in the right auricle. The main points of difference between the two were the less

frequent occurrence of lymphocytes and the more frequent thickening of the endocardium in the left auricle

In the sections of the ventricles there were no lesions of note except Aschoff nodules in one case. Increase in connective tissue or thickening of the arteries was not noted except in one case in which there was slight thickening and fibrosis of the larger arterioles.

The sections stained for fat showed accumulation of small fat droplets in the muscle fibers of both auricle and ventricle in five cases, and

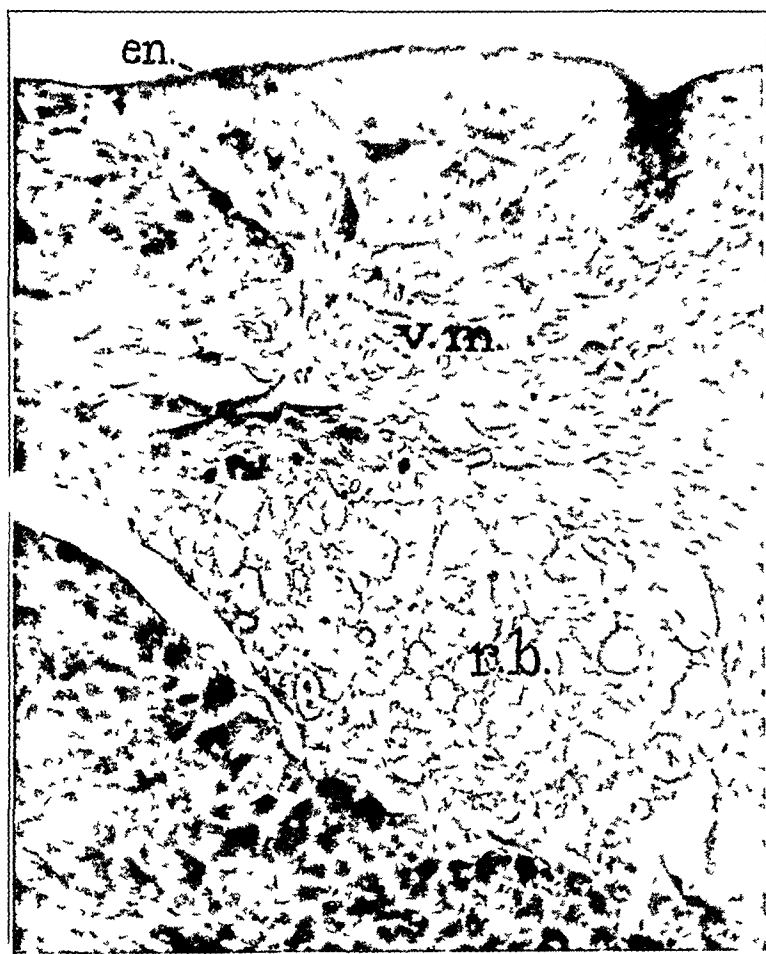


Fig 10—Through the “moderator band” of the right ventricle, showing the small right bundle branch, *r. b.*, in cross-section, surrounded by the ventricular muscle, *v. m.*, and lying some distance beneath the endocardium, *en.* ( $\times 150$ )

in general the amount of fat was approximately the same in the auricle and ventricle. In one case there was a moderate accumulation of fat droplets in the auricle and none in the ventricle. In three cases there was no demonstrable fat in either auricle or ventricle.

*Goiter*—There were six cases of exophthalmic goiter and two of adenomatous goiter with hyperthyroidism. Of the cases of exophthalmic goiter, four occurred in men and one in a woman. The ages of the patients ranged between 58 and 72, except one (32 years). Only one

died directly of cardiac decompensation. The largest heart weighed 423 Gm. One patient had coronary sclerosis, graded 3. Both of the patients with adenomatous goiter were women, one aged 60 and one aged 49. Both had hypertension in addition to thyrotoxicosis. One died following embolectomy of a femoral artery, the other died of cardiac decompensation three days after subtotal thyroidectomy. One heart weighed 463 Gm, the other 357 Gm. The exact duration of the auricular fibrillation could not be ascertained in any case. The histologic alterations of this group were even less marked than in the group with endocarditis. The sino-auricular node showed few changes. In one, the fibers were swollen and pale, corresponding with the auricular muscle fibers. In one, the muscular coat of the nodal artery was moderately thickened, but was without fibrosis. In another, as the end of the node was reached, there appeared a loose network of connective tissue with a few scattered small lymphocytes. The auriculoventricular node apparently was normal in all but one case, in which there was slight fibrosis of the nodal artery. In one case the bundle of His was more vascular than usual, and in another it was markedly congested, this condition involved the adjacent region of the interventricular septum also. The fibers of one were separated into definite fasciculi and were pale, some were swollen, and others were shrunken. The bundle branches were all normal except that in one case, at the origin of the right branch, there was in one area a small group of polymorphonuclear leukocytes with a few histocytes, the right branch was recognized, however, in only two cases. The muscle fibers of the right auricles did not show more changes than are usually seen in a similar group of normal hearts. In two cases the fibers were swollen and pale with prominent myofibrils and indistinct cross-striations, in two they were not swollen but the fibers had prominent myofibrils and invisible cross-striations, and in two the fibers were cloudy or homogeneous without visible cross-striations. In one case there were some small lymphocytes in the subepicardial fat, near the sino-auricular node, and some connective tissue replacement of the muscle fibers, and in three there were a few small lymphocytes in the epicardium near the node. In general, the muscle fibers of the left auricle were similar to those of the right, although they were not swollen as often. The ventricles showed few features of note. In the case of toxic adenoma there was an area of calcification in the membranous septum and an area of infarction in the left ventricle, and the cross-striations were distinct only in the left ventricle. A few small lymphocytes, polymorphonuclear leukocytes and plasma cells were present in the edematous subepicardium of the right ventricle in one case, and a few small lymphocytes and plasma cells in the subendocardium of the right ventricle in another. In one case there were a few small lymphocytes in the epicardium of the left ventricle. The ventricular muscle

fibers of one heart appeared to be slightly granular, with prominent myofibrils. Demonstrable fat was not present in the muscle fibers of the auricle in two cases, a mild to moderate amount, in three, and patchy, heavy infiltration in two. The ventricles showed little if any visible fat in all cases and a mild to moderate amount of lipochromatic pigment in five.

*Hypertension*—Six hearts were studied. In one there was evidence of old mitral endocarditis, which, however, had produced hardly any distortion of the valve, and in another there was coronary sclerosis, graded 3. Four of the patients were men and two were women, ranging in age from 42 to 81 years. Four died directly of cardiac decompensation, one of decompensation and grand mal, and one of mesenteric thrombosis complicating decompensation. Auricular fibrillation was known to have existed more than nine months in one case and more than two years in another. In the remainder, its duration was not known. The smallest heart weighed 410 Gm and the largest, 795 Gm. Inspection did not reveal abnormal fibrosis in any case. The sino-auricular node had thickened arterioles with reduction of their lumina in one case, in one case the arterioles were slightly thickened, and in another they were questionably thickened. The walls of some of the larger arterioles were thickened in one case. In the auriculoventricular node of one heart the arterioles were thickened, with almost obliterated lumina, and in the same node the larger vessels showed subintimal fibrosis. In one case the media of the arteries was somewhat thickened, and in another there was some fibrosis of the media of the main nodal artery. The vessels of the auriculoventricular bundle were not thickened in any case, but there were many blood vessels and much adipose connective tissue (50 per cent) in one, and in the criss communis of another there was some increase in the fat. The bundle branches did not show anything of note, the right bundle branch was recognized in five instances. A few small lymphocytes were present in the epicardium or subepicardium of the right auricle, in the region of the sino-auricular node, in four hearts, and were grouped near some of the larger arterioles in one of these. In one case, there were groups of small lymphocytes in the subendocardium, near the same node. The cross-striations of the muscle fibers of the right auricle were indistinct in two cases, and in two the fibers were swollen and pale. The arterioles of the right auricle were slightly thickened in one case. A patch of calcium deposit was present in the base of one mitral valve. The muscle fibers of the left auricle were swollen, with prominent myofibrils in one case, and the cross-striations were not visible in another. The endocardium was somewhat thickened in one left auricle, in another heart there were some small lymphocytes in the epicardium. The arterioles were slightly thickened in the ventricles in two cases, and there was some increase in

fibrous connective tissue in the interventricular septum in another. Deposits of calcium were present along the lower edge of the membranous septum in one heart. An appreciable increase of connective tissue was not present in any case. Fat was not visible in the muscle fibers in either auricle or ventricle in three cases, or in the auricle of one other case in which there was a slight amount in the ventricle. In one case there were patches of fatty change in both auricle and ventricle and moderate diffuse infiltration of the fibers of both auricle and ventricle in another. Lipochromatic pigment was not prominent in any case, but was seen in a small amount in two cases.

*Coronary Sclerosis*—Two cases were studied. One patient was a man, aged 70, who died of pyelonephritis following prostatectomy, he also had hypertension. The heart weighed 552 Gm, and the coronary sclerosis was graded 4. The other was a woman, aged 72, who died of empyema of the gallbladder associated with cardiac decompensation, she also had hypertension. The heart weighed 290 Gm, and the coronary sclerosis was graded 3. The fibrillation apparently had existed for some time in both cases. In one of these the artery of the sino-auricular node was somewhat thickened, and there was some subintimal fibrosis. In the other, the nodal artery showed moderate thickening of the intima, the fibers of the node were larger than usual, resembling more nearly cardiac muscle, and in the substance of the node were some groups of large histiocytes full of dark brown pigment granules, with scattered small lymphocytes in other parts. The auriculoventricular node of one had a nodal artery somewhat thickened with subintimal fibrosis, and the artery of the other also showed thickening of the intima. A tiny bit of calcium was present in the fibrous septum in the region of the left bundle branch in one case. The bundle branch appeared normal in one case but was not seen in the other. In the right auricle of one heart the cross-striations were not visible, in the other the myofibrils were unusually prominent, and there was an increase in intercellular connective tissue in the region of the sino-auricular node. The left auricle was similar to the right in both cases. The ventricular muscle fibers were swollen, and there were indistinct cross-striations in one heart. A moderate degree of fatty change was present in the muscle fibers of both auricle and ventricle in one case, but in the other case a change did not occur in either.

*Syphilis*—The patient was a woman, aged 35, who had a definite syphilitic infection of the central nervous system and the classic signs of aortic regurgitation. She died suddenly during a course of anti-syphilitic treatment. The arrhythmia was apparently of long standing. The heart was markedly enlarged with severe syphilitic involvement of the aorta and aortic valves. Considerable coronary sclerosis and dilatation of the left ventricle were present. The sino-auricular node and

the auriculoventricular node appeared normal. The left bundle branch appeared normal also, but its origin was surrounded by many small lymphocytes and a few plasma cells. These cellular elements were seen in the connective tissue in all of the sections showing the interventricular septum and were most numerous about some of the arteries; they were less numerous in the other sections of the ventricles. In one area, between the membranous septum and the auricular muscle were a number of small lymphocytes and a few plasma cells. In the connective tissue of the left auricle, especially in the subepicardial fatty tissue, were a great many plasma cells, some of which had two or three small nuclei; there were also some large pale cells undergoing mitotic division. The auricular and ventricular muscle fibers appeared normal. There was practically no fat in the muscle fibers of either auricle or ventricle.

*Terminal Fibrillation*—One of the patients was a man, aged 29, with Hodgkin's disease; the other was a man, aged 57, who died of a traumatic subdural hemorrhage. The fibrillation in both cases developed a short time before death. Both of the hearts appeared grossly normal, except for some dilatation of the right auricle in each. The two hearts, microscopically, showed little of note. There was apparently an increase of fibrous tissue in the sino-auricular node in one heart; the auricular fibers in this case were swollen and pale with clear centers, prominent myofibrils and indistinct cross-striations. A little fat was present in the muscle fibers of the auricles and ventricles of both hearts. Lipochromatic pigment at the nuclear poles was seen in small amounts in one case.

*Auricular Flutter*—Two cases were studied. Both patients were women, one 58 years of age and the other 65. Both had had hypertension for years and had died of cardiac decompensation. One had an adenomatous goiter also, which was believed to be toxic. The heart of this patient weighed 417 Gm., and that of the other 684 Gm. Except for a few small lymphocytes beneath the epicardium near the sino-auricular node and adipose connective tissue (50 per cent) in the *crus communis* of the bundle of His near the origin of the two bundle branches, one heart appeared to be normal in every respect. The other likewise showed little of note.

*Paroxysmal Tachycardia*—The heart studied was that of a man, aged 78, who had had paroxysmal tachycardia for twenty years. He died of pyelonephritis following cauterization of an epithelioma of the base of the bladder. This case is referred to also in the analysis of cases under paroxysmal tachycardia. The heart weighed 465 Gm. and appeared normal except for a small terminal vegetation on the mitral valve. The sections did not show abnormalities of note, except for the presence of a small deposit of calcium high up in the central fibrous body near the auriculoventricular node, with a few small lymphocytes and plasma

cells nearby. A moderate amount of lipochromatic pigment was present at the poles of the nuclei of the ventricular muscle fibers.

*Nerve Cells*—A special study was made to determine whether there were any changes in the nerve cells or ganglions in the region of the sino-auricular node. Sections containing nerve cells or ganglions were stained with thionin in eight supposedly normal hearts and in thirteen of the cases of auricular fibrillation. No difference in this respect was observed between the normal and pathologic hearts.

#### COMMENT

Several points with reference to the fundamental basis of auricular fibrillation in the series of 145 necropsies warrant emphasis. Chronic endocarditis, exophthalmic goiter and adenomatous goiter with hyperthyroidism were the three conditions most frequently encountered, representing 19, 25 and 19 per cent, respectively, of the entire number of cases, or a combined total of 63 per cent. The high incidence of cases of goiter is due in part to the fact that many of them were drawn from a large surgical goiter clinic. The percentage of cases of endocarditis is perhaps far too low because of the policy of returning patients with this condition to their homes if they cannot be materially benefited by treatment in hospital. Therefore, those on whom necropsies were performed were usually those who were too ill to be returned home. Nevertheless, these percentages indicate the types of heart disease in which auricular fibrillation is most likely to occur. Of the three conditions, endocarditis is perhaps most readily diagnosed by the average clinician, so that in the absence of evidence of endocarditis, one should next consider the possibility of hyperthyroidism.

Heart disease due to hypertension constituted 8 per cent of the cases if only those cases are included in which hypertension was known to have existed. This figure becomes 10 per cent, if the three cases are added in which the previous existence of hypertension could not be established. The average size of these hearts was much larger than those in the cases of hyperthyroidism, and in the absence of evidence of endocarditis or hyperthyroidism, hypertension should be considered as an etiologic factor when there is auricular fibrillation and a considerably enlarged heart, even though the hypertension cannot be established. Coronary sclerosis, chronic adhesive pericarditis and syphilis are rather unusual sources of auricular fibrillation.

In about 8 per cent of the cases there were two distinct etiologic factors. Although both contributed to the breakdown of the heart, it was usually one which caused the initial strain and the other which served as the "straw that broke the camel's back." When hypertrophy of the heart in a case of hypertension is accompanied by severe coronary sclerosis, it is logical to assume that the hypertension existed for a long

time prior to the development of the coronary sclerosis, because continued hypertrophy is not consistent with an impaired coronary circulation. A relatively common combination of etiologic agents in this group seems to be toxic adenomatous goiter and hypertension. Both of these conditions may exist a long time before injury to the heart is demonstrable, and it is usually impossible to decide which is the more important as regards the development of the cardiac condition. There is no question, however, that removal of the toxic adenomas, if possible, is of great advantage to the overburdened heart.

Except for the eleven cases of terminal auricular fibrillation, a condition which is not of great practical importance, there still remained a group of about 9 per cent of cases of established fibrillation in which a cause for the cardiac condition was not apparent. In most of these the status of the heart was considered to be of secondary importance to some more serious condition. In fact, cardiac symptoms were often mild.

From the small series of cases of auricular flutter, conclusions cannot be drawn as to the incidence in different types of heart disease. Endocarditis, hyperthyroidism and hypertension were the only definite types observed. One of the two cases of paroxysmal tachycardia, like the majority of such cases, occurred in a heart which had been subject to none of the etiologic factors in heart disease. The other was an unusual case of extensive myocardial fibrosis in a young adult.

The microscopic study of the twenty-nine hearts which had been the seat of these arrhythmias was strikingly negative as regards any distinctive lesion or, in fact, as regards any changes which could be assigned as the cause of the arrhythmia in any individual case. This was true not only for the types of arrhythmia, but also for the different types of heart disease. The lesion which Frothingham called attention to, namely, edema and vacuolization of the auricular muscle fibers, was observed about as often in the control group as in the affected hearts. On the whole, there was more evidence of disease in the region of the sino-auricular node than in other places, but even this was only slight or moderate in degree. The region of the orifices of the venae cavae has been called the sewer of the heart because of the frequently observed lesions there. None of the severe lesions of the sino-auricular node, such as cellular infiltration, degeneration or sclerosis, which were observed by some of the earlier investigators, was noted in this series.

If one accepts the conclusion drawn from this study that a specific histologic picture of auricular fibrillation or allied arrhythmias does not exist and further accepts the work of Lewis on the physiology of these arrhythmias, hypotheses are then in order concerning their cause. That there is a common cause in most cases of auricular fibrillation seems evident from the results of treatment by quinidine which is



apparently of similar efficacy in different types of heart disease, except perhaps in cases with hypertension. It is difficult to conceive that quinidine could alter the structure of the cells, at least as quickly as it sometimes acts. Some change possibly occurs in the chemical or physiochemical composition of the muscle fibers, at least in auricular fibrillation, which increases their refractoriness and causes reduction in the rate of conduction of an impulse. Possibly some vagal effect may cooperate with such change to bring about these conditions. Why the auricles and not the ventricles should fibrillate is another point to be considered, and this feature is the one which probably led Koch and others to attach such importance to the effect of dilatation of the right auricle. Furthermore, one has also to explain why the main path of the circus movement should be the region about the mouths of the venae cavae. This is probably due to some anatomic factor. Again, it is not easy to account for the occurrence of fibrillation in compensated cardiac conditions as well as in decompensation, and paroxysmal fibrillation and flutter befog the issue even more. All that can be said at the present time is that there is some unknown factor or a number of factors which bring about an identical disturbance in function of the auricular muscle fibers without associated structural changes.

#### SUMMARY AND CONCLUSIONS

A series of 145 cases of auricular fibrillation, 7 cases of auricular flutter, and 2 cases of paroxysmal tachycardia, all with necropsies, was studied from the standpoint of etiology and pathology. All the usual types of heart disease were found, cases of endocarditis and hyperthyroid states were the most numerous. Hypertension was found to be a common condition, but the occurrence of auricular fibrillation in other types of heart disease was uncommon. In about 8 per cent of the cases of auricular fibrillation there was a combination of possible etiologic factors, and in about 9 per cent an etiologic factor could not be suggested.

Twenty-nine hearts which had been the seat of these arrhythmias were studied microscopically. A distinctive lesion for the arrhythmia was not found, and the lesions were not considered in themselves of sufficient importance to account for the arrhythmia. There apparently is not, therefore, a specific histologic syndrome in auricular fibrillation and probably none in auricular flutter and paroxysmal tachycardia.

# THE VARIABILITY OF BLOOD PRESSURE

## MORNING AND EVENING STUDIES<sup>\*</sup>

H S DIEHL, M D

MINNAPOLIS

Studies such as those recently made by Alvarez,<sup>1</sup> and Diehl and Sutherland,<sup>2</sup> in which a surprisingly large number of presumably normal young adults are reported with elevation of blood pressure, lead one to wonder what proportion of these high readings can be attributed to normal fluctuations or variations of the blood pressure. Unquestionably many of the persons who show high pressures during required examinations of a group usually give normal readings, in fact, by taking repeated readings of the blood pressure of those university students who, on entrance examinations, had systolic pressures of 140 mm or more, Diehl and Sutherland<sup>2</sup> found that the pressures of only 15 per cent of this group persisted at that high level. Other students showed high readings on some occasions and low readings on others, while the largest proportion were above "normal" on only the initial reading. In all groups, however, there were sufficient variations of pressure to raise the following questions. Is it normal for young adults to have these fluctuations of blood pressure and how much fluctuation is necessary to constitute an abnormality?

Peters<sup>3</sup> concluded, from observations on blood pressure in 1,500 subjects, that in healthy persons less than 20 years of age the normal systolic pressure may vary from 60 mm plus one-half the age to 100 mm plus one-half the age, and that in persons more than 20 years of age the variation may be from 90 mm plus one-half the age to 130 mm plus one-half the age. In other words, he feels that in young people an individual variation of 40 mm is within normal limits. Hare<sup>4</sup> studied individual variations by taking four consecutive readings of the blood pressure after his subjects had rested for twenty

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<sup>\*</sup> Submitted for publication, Dec 27, 1928

<sup>\*</sup> From the Students' Health Service and Department of Preventive Medicine, University of Minnesota. This study was carried on with the aid of a grant from the Research Fund of the University of Minnesota.

1 Alvarez, W C, Wulzen, R, and Mahoney, L J. Blood Pressure in Fifteen Thousand University Freshmen, *Arch Int Med* **32** 17 (July) 1923

2 Diehl, H S, and Sutherland, K H. Systolic Blood Pressures in Young Men, Including a Special Study of Those with Hypertension, *Arch Int Med* **36** 151 (Aug) 1925

3 Peters, J T. Die Diagnostik von Hypertension bzw Hypertension des systolischen und diastolischen Blutdruckes, *Munchen med Wchnschr* **72** 503 (March 27) 1925

4 Hare, D C. The Variations of Blood Pressure Readings Studied Under Uniform Conditions, *Proc Roy Soc Med* **19** 36, 1926

minutes on a couch. The first reading was discarded and the variation between the next three readings computed. With sixty patients in 228 sittings, he found between the three readings a variation of more than 10 mm in 29.4 per cent of the sittings, of 15 mm or more in 11.9 per cent and of 20 mm or more in 1.3 per cent. Brooks and Carroll<sup>5</sup> found the maximum pressure of the day between four and five o'clock in the afternoon and, after a night's sleep, an average drop of 16.5 mm in thirty patients with a mean pressure of 100 mm, a drop of 24 mm in sixty-eight patients with a mean pressure of 142.5 mm, and a drop of 44.8 mm in twenty-nine patients with a mean pressure of 204.5 mm. Kinney,<sup>6</sup> in discussing factors which influence blood pressure, stated that blood pressure frequently does not run a "constant course but jumps about the scale in an erratic manner," and that this condition is not limited to persons of a nervous temperament. Sigler<sup>7</sup> cited several cases of hypertension with systolic pressures showing variations of from 30 to 65 mm, he stated that "it would seem that variations of this kind, as well as hypertension in general, are dependent upon some structural or functional abnormality of the vegetative nervous system exhibiting itself in the form of vasomotor pressor effects." Luisada<sup>8</sup> noted in normal persons a nocturnal lowering of systolic pressure of from 15 to 20 mm and a simultaneous rise of from 10 to 20 mm in diastolic pressure. Hourly variations, he said, may differ in intensity in different circulatory syndromes and in different illnesses.

#### EXPERIMENTAL PROCEDURE

*Technic*—These studies of the variability of the blood pressure, which answered some questions and raised others, led me to undertake some additional observations on variation in blood pressure in normal persons under normal conditions. The group studied consisted of 100 male students of the University of Minnesota. Readings were taken in the morning and evening of each day for six consecutive days. The morning readings were made between the time of rising and that of breakfast, the intent being to record the pressure at the beginning of the day's activity, not necessarily the minimum pressure for the day. The evening readings were taken just before dinner, at the close of the day's activity. Readings were made with the subject sitting on a chair. Three senior medical students assisted in taking the readings but each observer took all readings on the cases assigned to him, and identically the same technic was followed by each one. Mercury manometers and the auscultatory method were used throughout.

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5 Brooks, H., and Carroll, J. H. A Study of the Effects of Sleep and Rest on Blood Pressure, *Arch Int Med* **10** 96 (Aug.) 1912

6 Kinney, V. C. Blood Pressure. Some Original Observations, *J A M A* **83** 1420 (Nov 1) 1924

7 Sigler, L. H. Periodic Variability of Arterial Hypertension, *Am J M Sc* **172** 543 (Oct.) 1926

8 Luisada, A. Le variazioni orarie della pressione arteriosa, *Riforma med.* **41** 817 (Aug 31) 1925

*Analysis of the Group*—The 100 students on whom the observations of the present study were made were unselected except in that they all belonged to fraternities, and a considerable proportion of them were medical students. The readings all were made at the fraternity houses. The mean age of the group was  $22.71 \pm 0.17$  years, the mean weight,  $148.00 \pm 0.64$  pounds, and the mean height,  $68.52 \pm 0.196$  inches. Taking as the pressure for each student the average of all the readings taken on him, the mean pressure for the group was  $119.15 \pm 0.47$  mm. In studies of the blood pressure of freshmen entering the university, Diehl and Sutherland<sup>2</sup> found in the age group of 22 years a mean systolic pressure of  $122.6 \pm 0.50$  mm and in that of 23 years a mean pressure of  $123.3 \pm 0.67$  mm. In students with a mean age of  $20.078 \pm 0.046$  years, Jackson<sup>9</sup> found a mean weight of  $141.44 \pm 0.29$  pounds and a mean height of  $68.684 \pm 0.042$  inches. From these comparisons it would seem that the present group was not abnormal in any way but was truly representative of the older portion of the university students.

*Morning Pressures*—As previously stated, the morning readings of pressure were made on each of six consecutive days at the beginning of the day's activity. The mean of these morning systolic pressures in the 100 subjects was  $114.94 \pm 0.34$  mm. As a measure of the variability of the morning pressure in an individual subject, the standard deviation from the mean of the six morning readings taken on the case was computed. Then the mean of all these morning standard deviations for the 100 subjects was calculated and found to be  $5.57 \pm 0.167$  mm, the mode was 4.5 mm and the median, 5.25 mm. The distribution of the morning standard deviations is shown in chart 1 A.

The range of blood pressure, that is, the difference between the lowest and the highest readings, although not an accurate statistical measure, was computed because it is in these terms that the average practitioner thinks of variation in blood pressure. The morning range in individual cases has been portrayed graphically in chart 2 A. The lowest morning range over the six day period was 1 mm, the highest, 39 mm, the mean,  $16.29 \pm 0.486$  mm, the mode, 16 mm, and the median, 16 mm. With the mean, mode and median so nearly identical for both range and standard deviation, the distribution curves are regular and probably truly representative for such a group.

*Evening Pressures*—The evening pressures were taken at the end of the day's activity and for the group as a whole showed a mean pressure of  $124.37 \pm 0.29$  mm. The standard deviations of the evening

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<sup>9</sup> Jackson, C. M. The Physique of Male Students at the University of Minnesota. A Study in Constitutional Anatomy and Physiology, *Am J Anat* **40** 59 (Sept 15) 1927.

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9 Jackson, C. M. The Physique of Male Students at the University of Minnesota. A Study in Constitutional Anatomy and Physiology, *Am J Anat* **40** 59 (Sept 15) 1927.

readings from the evening mean of each subject are shown in a distribution chart, chart 1 *B*. The mean of all these individual evening standard deviations was  $5.86 \pm 0.21$  mm, the mode, 3.5 mm, and the median, 6 mm.

The minimum evening range in any subject was 2 mm, the maximum, 38 mm, the mean,  $17.86 \pm 0.616$  mm, the mode, 22 mm, and

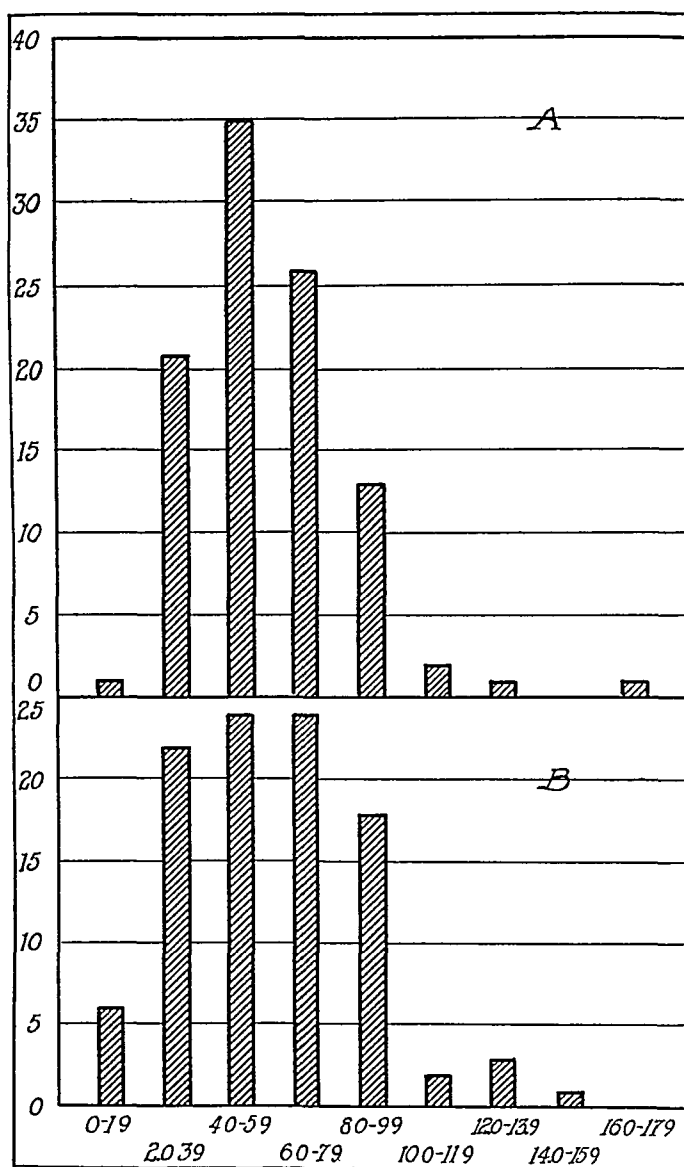


Chart 1—*A* gives the standard deviation of the six morning readings on each subject from the mean of these six readings, *B*, the same for the evening readings. The vertical scale at the left indicates the number of subjects.

the median, 16 mm. Chart 2*B* shows the distribution of the range in evening blood pressure in the individual subjects.

*Comparison of Morning and Evening Readings*—The mean of the morning readings was  $114.94 \pm 0.34$  mm and of the evening readings,

124.37  $\pm$  0.29 mm, a difference of 9.43  $\pm$  0.44 mm. Since the actual difference shown is more than twenty times the probable error of the difference, the significance of the observation is beyond question and indicates that in this group the day's activity tended to increase the systolic blood pressure 9.43  $\pm$  0.44 mm. In a study of recruits at Camp Lewis, Addis<sup>10</sup> found a mean pressure, in bed, of 99 mm, with an increase to 127 mm during the day's activities.

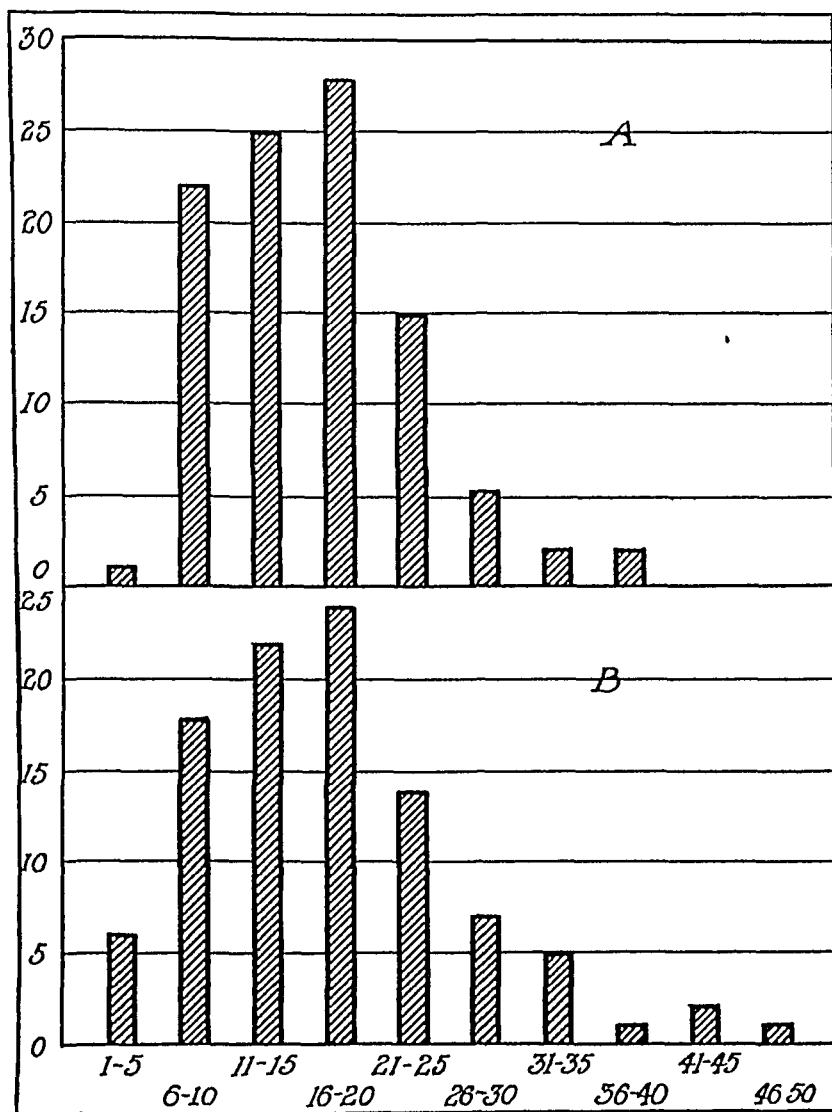


Chart 2—*A* gives the range in morning readings of blood pressure on the individual subjects, *B*, the range in evening readings. The vertical scale at the left indicates the number of subjects.

The standard deviation from the mean of all morning readings was 12.27  $\pm$  0.34 mm and of all evening readings, 10.47  $\pm$  0.30 mm. The difference is 1.80  $\pm$  0.45 mm, with the morning deviation the greater.

10 Addis, T. Blood Pressure and Pulse Rate Levels, the Levels Under Basal and Daytime Conditions, *Arch. Int. Med.* **29**:539 (April) 1922.



The mean of the standard deviations in the individual cases was  $5.57 \pm 0.167$  mm for the morning series and  $5.86 \pm 0.21$  mm for the evening series, a difference of  $0.29 \pm 0.27$  mm. These comparisons indicate that in the group as a whole, the morning readings show a slightly greater variability from the group mean than do the evening readings, but that the average variability in individual subjects is practically the same for morning and evening. In other words, the day's activity tends to bring the blood pressure of the group closer together, but has no appreciable effect on the individual variability.

The average range of systolic blood pressure over the period of six days was  $16.29 \pm 0.486$  mm in the morning and  $17.86 \pm 0.616$  mm in the evening, again indicating that, although the readings were somewhat lower in the morning, the variability in the morning is practically as great as the evening.

The difference between morning and evening readings was computed for each day and the average of these differences, without regard to sign, for six daily examinations was called the "mean difference" for the case. This mean difference, of course, does not indicate whether the morning or evening pressure was higher. The average mean difference for the 100 cases was  $12.69 \pm 0.42$  mm, the modal mean difference, 13.5 mm, the median, 12 mm. It appears that the average difference between morning and evening pressure is less than the average range over a period of six days in either the morning or in the evening.

Although the mean of all evening readings was  $9.43 \pm 0.44$  mm higher than the mean of all morning readings, yet in the 100 cases the morning average was higher than the evening average in fifteen cases and the same as the evening average in one case. With the readings taken morning and evening for six days on each of the 100 cases there were approximately 600 "pressure days." Of these, the morning readings were higher in 135 and the evening readings higher in 445, the two were identical in twenty.

*Total Variation*—The mean of all readings, without regard to time, was  $119.76 \pm 0.244$  mm (differing slightly from the mean of the means of individual subjects,  $119.15 \pm 0.47$  mm, because, in a few instances, five instead of six evening readings were taken, due to the absence of students from the house), with a standard deviation from the mean of  $12.28 \pm 0.17$  mm. The mean of all the readings in each case, morning and evening, was computed and the standard deviation from this mean was considered the "standard deviation of the total readings." The mean of all these "standard deviation of the total readings" in individual cases was  $8.67 \pm 0.20$  mm, the mode, 7 mm, and the median, 9 mm. The total range of a subject is the difference between the lowest and the highest of the twelve readings, irrespective of whether they were taken in the morning or in the evening. The mean of these "total ranges"

was  $27.47 \pm 0.87$  mm, the mode, 26 mm, and the median, 26 mm. This mean total range is surprisingly high, in view of the mean morning range of  $16.29 \pm 0.489$  mm and the mean evening range of  $17.86 \pm 0.616$  mm.

## RELATION OF VARIABILITY TO MEAN PRESSURE

It has frequently been suggested by writers on the subject of blood pressure that repeated transient elevations of blood pressure probably

*The Distribution of Mean Pressures and Case Standard Deviations in Individual Subjects*

Mean Pressure	Standard Deviations																Total
	0 to 0.9	1 to 1.9	2 to 2.9	3 to 3.9	4 to 4.9	5 to 5.9	6 to 6.9	7 to 7.9	8 to 8.9	9 to 9.9	10 to 10.9	11 to 11.9	12 to 12.9	13 to 13.9	14 to 14.9	15 to 15.9	
1 Morning Readings																	
90-94			1														1
95-99		1	2		2		1										6
100-104			1		4	1				2							8
105-109			3	1	4	4	2				1	1	1				17
110-114			4	2	2	3	4	5	4	1						1	26
115-119				2	3	2	2	1	1								11
120-124				1	3	1	2	3	1	1							12
125-129			2	1	1	1	1	2	1								9
130-134					1	1		2	2								6
135-139				1		1											2
140-144					1		1										2
Total	0	1	13	8	21	14	13	13	9	4	1	1	1	0	0	0	100
2 Evening Readings																	
105-109										1							1
110-114					1	1		2									8
115-119	1	1	3	1	4	5	3	1	2	1			1				23
120-124	1	1	3	6	5	2	2	3	3	1			1			1	30
125-129	1	1		2	1	3	1	4	2	2							17
130-134		1	1	1	1	3	1		1	1				1			11
135-139			1			1	2		1	1							5
140-144					1	1	1	1		1							5
Total	3	4	10	12	9	15	12	11	9	9	1	1	1	2	0	1	100
3 All Readings																	
105-109							2		1	3	1						7
110-114					3		2	2	5	5	1						26
115-119					1	3	2	10	1	6	4	2	2	1		2	32
120-124					1		1	1	1	2	2					1	9
125-129				2		3	1	2	2	2							12
130-134			1					2			1				1	1	6
135-139					1		2	1	2	1							7
140-145						1											1
Total	0	0	1	2	6	7	10	18	12	19	9	4	4	2	2	4	100

represent the first stage of a persistent hypertension<sup>11</sup>. If this is true one would expect a person's mean blood pressure to increase more or less in proportion to the increase in variability. In this study the mean

11 O'Hare, J. P., and Walker, W. G. Arteriosclerosis and Hypertension, Arch Int Med **33** 343 (March) 1924. Von Monakow, P. Blutdrucksteigerung und Niere, Deutsches Arch f. klin. Med. **133** 129 (Aug.) 1920. Lord Dawson of Penn. Discussion of Hypertension, Proc. Roy. Soc. Med. **19**, 27 (Jan. 25) 1926. Herrick, W. W. Examination of the Circulatory System, the Importance of High Blood Pressure, Internat. J. Med. & Surg. **39** 507 (Dec.) 1926.

pressure in each case is computed for a series of from ten to twelve readings, and the variability in each case in this series is measured by the standard deviation of the case. A test of the relationship of these two factors was made by calculating the coefficients of correlation.

Chart 3 shows the distribution from which these correlation coefficients were computed. For the morning readings of blood pressure the correlation coefficient between the height of the pressure and its standard deviation was  $0.126 \pm 0.066$ , for the evening readings, the correlation coefficient was  $0.049 \pm 0.067$ , and for all readings taken in the case, irrespective of time, the correlation coefficient was  $-0.204 \pm 0.065$ . One can conclude, therefore, that for the morning readings there is no signifi-

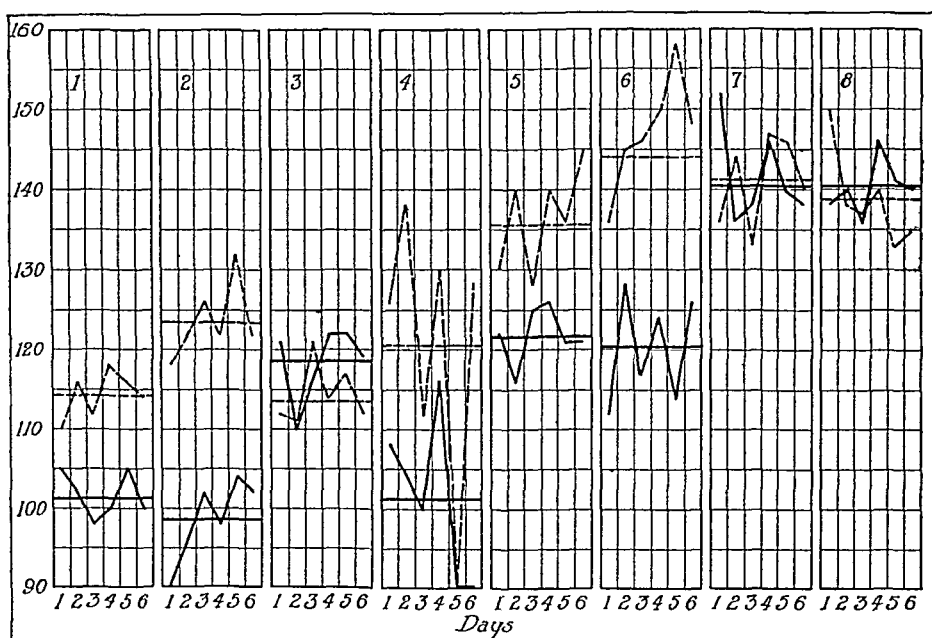


Chart 3—The variation in blood pressure in morning and evening readings on eight subjects, during a period of six days. The solid line represents the readings taken in the morning, the broken lines, those taken in the evening. The vertical scale at the left indicates millimeters of blood pressure.

cant correlation between the height of the pressure and its variability, that for the afternoon readings the probable error of the correlation coefficient is even larger than the coefficient itself, allowing no possible correlation, and that for all the readings on the subject there is a negative correlation coefficient which is approximately three times as large as its probable error. In other words, the tendency exhibited is toward a slight negative correlation between the height of the pressure and its variability, that is, as the blood pressure increases the variability decreases. The significance of the difference,

however is not sufficiently marked to justify any generalizations on the subject

#### BLOOD PRESSURE CURVES OF REPRESENTATIVE CASES

In cases 1 and 2 (chart 3) the morning and evening pressure curves run almost parallel with the evening pressures constantly higher. In case 3 the mean morning pressure is 4 mm higher than the mean evening pressure, although on two days the evening pressure is the higher and the variation from day to day is not great. Case 4 shows a great variation from day to day in both morning and evening pressures. In case 5 the evening pressure rises on one occasion to 145 mm and the mean evening pressure is 135.57 mm, while the morning pressure varies from 116 to 126 mm with a mean morning pressure of 121.83 mm. Case 6 presents a morning curve which would be considered normal, but an evening curve that might justifiably be called hypertension. Cases 7 and 8 show persistently high pressures with relatively little daily variation. Although in case 7 the mean evening pressure is the higher and in case 8 the mean morning pressure is the higher in neither case is there much difference between the morning and the evening mean.

#### COMMENT

Brooks and Carroll<sup>5</sup> Luisada,<sup>8</sup> MacWilliam<sup>12</sup> and others have pointed out that there tends to be somewhat of a daily cycle in blood pressure with the highest pressure occurring in the late afternoon and the lowest pressure occurring in the latter part of the night. The present study shows that in 100 apparently normal young adults this increase which occurs during the day's activities approximates 9.5 mm. Proof that this increase is gradual throughout the day will require further observations.

With the distribution curves for standard deviation and for range as regular as they are, it is probable that similar variations will be found in other groups of subjects and that some daily variation of this kind is "normal." Further weight is given to the suggestion that more or less variability is normal by the fact that there is no positive correlation between the mean height of a person's blood pressure and its variability. This same lack of correlation throws grave doubt on the suggestion frequently found in the literature that transient elevations of blood pressure in young persons represent the beginnings of a persistent hypertension in later life. Of course, there was no evidence that this group of students contained any potential or early true hypertensions. How-

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12 MacWilliam, J. A. Blood Pressure and Heart Action in Sleep and Dreams. *Brit. M. J.* 2: 1196 (Dec. 22) 1923.

ever, since Bell and Clawson<sup>13</sup> pointed out that, as a conservative estimate, 15 per cent of persons more than 50 years of age will die from hypertension (Fahr<sup>14</sup> gave 23 per cent), it is exceedingly unlikely that this group of 100 unselected young men should not contain approximately a proportionate number of them

Since this group, although unselected, includes a few persons who in this series of readings had a persistently high blood pressure, a question might arise in the minds of some readers as to whether or not this fact makes the group sufficiently abnormal to influence the data. However, as no positive correlation between the height of the blood pressure and the variability has been found, it can be said safely that the chance inclusion of these subjects did not in any way increase the variability found in the group as a whole

#### SUMMARY

1 Readings of the blood pressure of 100 male university students were made in the morning and evening of six consecutive days

2 The group was unselected and apparently of average height, weight and blood pressure

3 The mean morning pressure of all readings taken was  $114.94 \pm 0.34$  mm, and the mean of all evening readings was  $124.37 \pm 0.29$  mm

4 The standard deviation, which is the best measure of variability, was calculated for the morning readings and for the evening readings of each subject. For the 100 cases, the mean of the morning standard deviations was  $5.57 \pm 0.167$  mm, and of the evening standard deviations was  $5.86 \pm 0.21$  mm

5 The variation in blood pressure from day to day as measured by standard deviation and range is practically the same in the series of morning readings as in the series of evening readings

6 With an average morning blood pressure range of  $16.29 \pm 0.486$  mm, an average evening range of  $17.86 \pm 0.616$  mm and an average total range of  $29.47 \pm 0.87$  mm, it would seem that in any consideration of individual blood pressure readings the possibility of at least as much "normal" variation as this would have to be considered

7 Study of the individual cases shows that in some subjects the difference between morning and evening pressures is consistently great enough for the one to be considered normal and the other hypertension,

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13 Bell, E. T., and Clawson, B. J. Primary (Essential) Hypertension, *Arch. Path.* **5** 939 (June) 1928

14 Fahr, G. E. Hypertension Heart, *Am. J. M. Sc.* **175** 453 (April) 1928

and that in other cases the variation from day to day in the same person is sufficiently great for the pressure to be considered normal on one day and as hypertension on a subsequent day

8 A positive correlation was not found between the height of the blood pressure and its variability. This fact makes it seem unlikely that transient elevations of blood pressure in young persons represent the first stages of a persistent hypertension

# PEPTIC ULCER

A STUDY OF FIVE HUNDRED AND FIFTY-SIX CASES \*

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The past twenty years have witnessed a considerable advance in the knowledge of peptic ulcer. Credit for this is due chiefly to roentgenologists, who not only have simplified the diagnosis but have led to a better understanding of the pathologic physiology and complications of the disease. Therapy, especially surgical measures, likewise has improved. Diagnosis is made earlier, and most of the end-stages which occur when the ulcer is allowed to run its course are avoided. Yet the fundamental facts concerning peptic ulcer still are shrouded in mystery. There is much difference of opinion concerning the etiology, the cause and the nature of the symptoms. As long as this is so, there can be no unanimity of opinion regarding treatment.

Much of the disagreement on therapy depends also on the meager amount of statistical information in the voluminous literature on peptic ulcer. Many papers deal with the effect of a single form of treatment, often in a small number of cases, and usually with a short period of observation after the completion of the treatment. Evidence is scanty, and the conclusions are controvertible. Data are needed on a large series of carefully studied cases observed for a considerable period.

This paper deals with an analysis of the cases of patients with gastric and duodenal ulcer who have been admitted to the Peter Bent Brigham Hospital from its opening in 1913 to September, 1926. All cases in which the patients were admitted to the medical service have been included. Through the courtesy of Dr. Harvey Cushing and the other members of the surgical service, all surgical cases are included, with the exception of those of one member of the surgical staff who had already planned to report his own cases. A few cases, approximately twenty-five, which are recorded as cases of peptic ulcer in the hospital records have been omitted because the symptoms and the roentgen observations were such as to raise a reasonable doubt as to the accuracy of the diagnosis.

With these omissions, the series consists of 556 cases, 407 patients were admitted to the medical wards, 149 directly to the surgical and 155 were transferred from the medical to the surgical wards for operation.

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\* Read in part before the Harvard Medical Society, Feb 14, 1928

A follow-up has been obtained on 460 patients (82.5 per cent). Seventy-six (13.6 per cent) of the total number are dead, from various causes, 264 (47.4 per cent) have been followed from their discharge to the present time, 120 (21.5 per cent) have been heard from at some time since discharge, but not recently, and ninety-six (17.5 per cent) have not reported. All patients were asked to return for a personal interview and examination, and an x-ray picture of the stomach. Those

TABLE 1—*The Incidence of Gastric and Duodenal Ulcers as Reported by Other Observers*

Authority	Source	Location of Ulcer	Number of Cases	Percentage with Ulcer
Brinton, W. <i>Ulcer of the Stomach</i> , London, J. & A. Churchill, 1857	Autopsy	"Peptic"	?	5
Howard, C. P. <i>M. News</i> , Philadelphia, 1904, vol. 85, p. 673	Autopsy	Gastric and duodenal	10,841	1.32
Dietrich, H. A. <i>Munchen med. Wehnschr.</i> 59: 683, 1912	Autopsy	Gastric and duodenal	8,543	1.5
Ophuls, W. <i>A Statistical Survey of 3,000 Autopsies</i> , Stanford Univ. Press, 1926, p. 263	Autopsy	Gastric and duodenal	3,000	2.2
Sturtevant, M., and Shapiro, L. L. <i>Arch. Int. Med.</i> 38: 41 (July) 1926	Autopsy	Gastric and duodenal	7,700	2.06
Lehman, H. <i>Mitt. a. d. Grenzgeb. d. Med. u. Chir.</i> 39: 185, 1926	Autopsy	Gastric and duodenal	1,000	20.2
Von Leube, quoted by von Ziemssen, <i>Cyclopedia of Practice of Medicine</i> , New York, 1874, p. 195	Autopsy	Gastric	13,005	4.8
Fenwick, S., and Fenwick, W. S. <i>Ulcer of the Stomach and Duodenum</i> , Philadelphia, P. Blakiston's Son & Company, 1900	Autopsy	Gastric	47,912	4.2
Martin, C. F., in Osler, W., and McCrae, T. <i>System of Medicine</i> , ed. I, Philadelphia, Lea & Febiger, 1908, vol. 5, p. 176	Autopsy	Gastric	59,450	4.4
Hemmeter, J. C. <i>Diseases of the Stomach</i> , Philadelphia, P. Blakiston's Son & Company, 1897, p. 495	Autopsy	Gastric	11,888	1.4
Sturtevant, M., and Shapiro, L. L. <i>Arch. Int. Med.</i> 38: 41 (July) 1926	Autopsy	Gastric	7,700	1.558
Martin, C. F., in Osler, W., and McCrae, T. <i>System of Medicine</i> , ed. I, Philadelphia, Lea & Febiger, 1908, vol. 5, p. 176	Autopsy	Duodenal	78,000	0.297
Fenwick, S., and Fenwick, W. S. <i>Ulcer of the Stomach and Duodenum</i> , Philadelphia, P. Blakiston's Son & Company, 1900	Autopsy	Duodenal	13,055	0.26
Cooley, E. D. <i>Illinois M. J.</i> 23: 187, 1913	Autopsy	Duodenal	38,106	0.41
Sturtevant, M., and Shapiro, L. L. <i>Arch. Int. Med.</i> 38: 41 (July) 1926	Autopsy	Duodenal	7,700	0.57
Martin, C. F., in Osler, W., and McCrae, T. <i>System of Medicine</i> , ed. I, Philadelphia, Lea & Febiger, 1908, vol. 5, p. 176	Clinical	Gastric	339,575	0.894
Howard, C. P. <i>M. News</i> , Philadelphia, 1904, vol. 85, p. 673	Clinical	Gastric	161,599	0.57
Lynch, R. <i>Canad. M. A. J.</i> 17: 677, 1927	Clinical	Peptic	944	1.45

who could not return to the hospital were reached by a letter, either directly or through their local physician or relatives. The duration of observation varied from six months to thirteen years, the average being slightly more than four years.

#### INCIDENCE

The number of patients with ulcer entering the medical service was 1.86 per cent of the total number of admissions to this service. This agrees fairly well with the incidence of ulcer as given by other observers, of which a few of the most representative figures are given in table 1.



With the exception of Brinton's 5 per cent and Lehmann's 20.2 per cent, there is little variation in the incidence of peptic ulcer. Post-mortem statistics for ulcer of the stomach apparently fall into two groups, those collected chiefly from sources from the continent (von Leube, the Fenwicks and Martin) and those from American sources (Hemmeter, and Sturtevant and Shapiro), the former averaging three times as much as the latter. The older papers show the clinical diagnosis of ulcer to be less common than the pathologic, but this has not been the experience at the Peter Bent Brigham Hospital. Present clinical observations differ also from the older pathologic reports in the relative incidence of gastric and duodenal ulcers. Whereas gastric ulcer used to be reported as more common than duodenal, the reverse is generally true today.<sup>1</sup> In this series there are 398 (71 per cent) cases of duodenal ulcer and 135 (24 per cent) cases of gastric ulcers.

Bolton<sup>2</sup> has quoted figures which suggest that there may be a wide variation in the regional distribution of ulcer. In an attempt to gain some information on this point, we have compared the relative incidence of the birthplaces of the patients in our series with those of all the patients admitted to the hospital. The close agreement between the two suggests that there is no racial difference in the susceptibility to peptic ulcer, unless it be somewhat higher among the Russian Jews.

Four hundred and five (72.8 per cent) of the patients were males and 151 (27.2 per cent) females. Of the patients with gastric ulcers, eighty-three were men and fifty-two were women, and of those with duodenal ulcer, 307 were men and ninety-one were women. Duodenal ulcers are generally regarded as occurring much more frequently in men,<sup>3</sup> but there is a conflict of opinion concerning gastric ulcers.<sup>4</sup>

Bolton<sup>2</sup> concluded that there was no sex difference.

In 18 per cent of our cases the patients had coexistent gastric and duodenal ulcers. Higher figures are given by Judd and Proctor<sup>5</sup> (16 per cent) and Perry and Shaw<sup>6</sup> (12.5 per cent).

1 Lynch, R. *Canad. M. A. J.* **17** 677, 1927. Eggleston, E. L. *Critical Review of 500 Cases of Gastric and Duodenal Ulcer*, *J. A. M. A.* **75** 1542 (Dec. 4) 1920. Mayo, W. J. *Gastric Ulcer*, *ibid.* **65** 1069 (Sept. 25) 1915.

2 Bolton, C. *Ulcer of the Stomach*, London, E. Arnold, 1913.

3 Martin, C. F., in Osler, W., and McCrae, T. *System of Medicine*, ed. 1, Philadelphia, Lea & Febiger, 1908, vol. 5, p. 176. Lynch (footnote 1, first reference).

4 Riegel, F., in Nothnagel. *Encyclopedia of Practical Medicine, Diseases of the Stomach*, Am. ed., Philadelphia, W. B. Saunders Company, 1903.

5 Proctor, O. S. *Surg. Gynec. Obst.* **41** 63, 1925. Judd, E. S., and Proctor, O. S. *M. J. & Rec.* **121** 93 (Jan.) 1925.

6 Perry, E. C., and Shaw, L. E. *Guy's Hosp. Rep.* **50** 171, 1893.

## AGE

The average age at which symptoms of ulcer were first noticed was 36.8 years (35.9 for males and 37.8 for females). The youngest patient was 6 years old, and the oldest was 80. Sixty-four and seven-tenths per cent of the cases occurred before the patients were 40.

Chart 1 shows the age at onset in five-year periods for both sexes. The curve is nearly symmetrical and is similar in appearance to those given by Ophuls,<sup>7</sup> Riegel<sup>4</sup> and Martin.<sup>3</sup> It would seem that ulcer as a disease of young adults has been stressed too much.

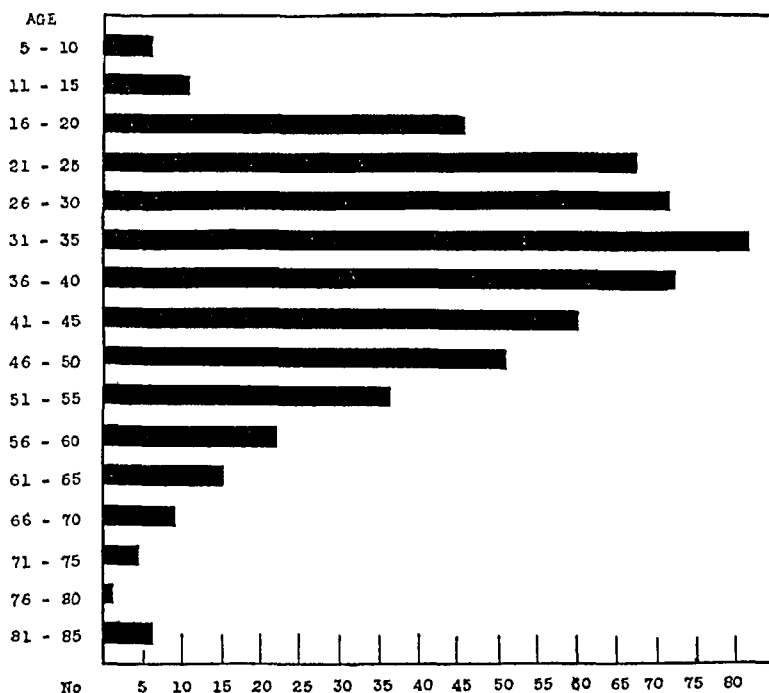


Chart 1—Age at onset of symptoms of ulcer

The question arises whether, in spite of the symmetrical curves which all obtain, the incidence of ulcer during the later years of life is not actually higher because the number of people in these age groups is less than in the earlier ones. This would seem to be answered in the negative by Ophuls,<sup>7</sup> who showed that the ratios of the cases in each age group remain rather constant after the third decade, from 2.2 to 3.2 per cent.

In 3 per cent of our series, symptoms of ulcers began before the patients were 15 years of age, and in 11.3 per cent before they were 20. Proctor<sup>8</sup> found an even greater incidence in childhood (4.2 per cent in his 2,000 cases).

<sup>7</sup> Ophuls, W. A Statistical Survey of 3,000 Autopsies, Stanford University, Stanford Univ. Press, 1926, p. 268.

<sup>8</sup> Proctor (footnote 5, first reference).

## OCCUPATION

The occupation of the patient has frequently been proposed as a factor in the etiology of peptic ulcer, although most students of the subject have been unable to find any connection between the two. This is equally true in this series in which the list of occupations numbered more than fifty and are not of related types. Since physical exertion also has been postulated as an etiologic factor, an attempt was made to classify all the cases according to the degree of muscular activity which the occupation of the patient entailed. Among persons in sedentary occupations (professional and executive men, office and clerical workers), ulcer occurred in 198, and of those in moderate occupations (skilled labor, factory workers, house workers, store keepers, etc.), in 235, and among those in strenuous occupations (unskilled labor, engineers, etc.), in 123. We do not have any figures as to the ratio of these occupations in the general hospital population, but have the impression that they are not far different, and that there is no connection between ulcer and exertion.

## FAMILY AND PAST HISTORY

There were only nine families in which peptic ulcer was known to exist, four members having died of it. In addition, there was a history of stomach trouble in thirty-seven which was fatal in nineteen cases. These figures do not suggest an hereditary tendency for ulcer, although Hurst<sup>9</sup> stated that he had seen it run in a few families, and Draper<sup>10</sup> was inclined to be more positive, describing a definite constitutional type for ulcer.

Thirty (5 per cent) of the patients had hypertension, and thirty-five (6 per cent) had generalized arteriosclerosis, an incidence no greater than would be expected in other persons (at the age periods). Smithies<sup>11</sup> found 14.7 per cent of his cases of gastric ulcer with these complications, but this seems too small a figure to warrant the assumption that they play any determining factor in ulcer, as has been claimed by Virchow<sup>12</sup> and later by Ophuls<sup>7</sup>. No other disease occurred frequently enough in the past history to suggest an association with ulcer.

## SYMPTOMATOLOGY

*Duration and Periodicity*—The average duration of symptoms at the time of entry was seven years. In many patients of course, symptoms

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9 Hurst, A. F. Brit M J **1** 559, 1920

10 Seegal, D., Draper, G., and Dunn, H. L. Human Constitution. Clinical Anthropometry, J A M A **82** 431 (Feb 9) 1924

11 Smithies, F. Am J M Sc **166** 781, 1923

12 Virchow, R. Virchows Arch f path Anat **5** 362, 1853. Wilson, C. B., and McDowell, I. E., Am J M Sc **13** 208, 1914

had existed for only a few days or months, in ninety-seven for less than a year. On the other hand, 63 per cent had had symptoms for more than two years, and in many the duration of the symptoms extended into decades. Six patients had had symptoms for from thirty-six to forty years. In cases of short duration a diagnosis frequently had not been made, but in many of long duration the cause had been recognized and the condition treated.

Almost all of the patients had experienced periods of relief from symptoms, which occurred as frequently without medical intervention as with treatment. The remissions were from a few months to a year in duration and usually exceeded the relapses. In a few patients there was a remission of ten years and in one of twenty years.

Five hundred and thirty-nine patients of the total 556 had some form of abdominal distress. Seventeen, or 3 per cent, had none, the ulcers being found post mortem or by roentgen examination. This is somewhat less than was formerly taught, namely, that in about 10 per cent of the cases of gastric ulcer and 20 per cent of those of duodenal ulcer the condition is symptomless.

One hundred and fifteen (20.6 per cent) of the patients who had distress said that it was slight, 322 (58 per cent), that it was moderate, and 102 (18.4 per cent), that it was intense.

In the great majority of patients (461) the pain was in the upper part of the abdomen. Those who had the most typical histories of ulcer placed it in the epigastrium, and those whose symptoms were more indefinite tended to name other regions.

The pain originated in the right lower quadrant in seven, and radiated there in five others. This is interesting in view of the increasing evidence of a physiologic relationship between the pylorus and the ileocecal region, and because a few patients enter the hospital every year who have had appendectomies done because of symptoms which are later shown to be due to peptic ulcer.

The pain was typically boring, grinding, gnawing or burning in only a few (136). Frequently it was not characterized except as "pain." In 282 there was a sense of fulness or distention in the abdomen, occasionally as the only distress, but often associated with belching. "Gas" was also one of the commonest symptoms, occurring in 392 cases, but its significance is difficult to estimate, for it occurs so frequently without ulcer. Its frequency in this series suggests that intestinal disturbances of a functional nature were also present.

Radiation of the pain occurred in approximately 104 cases. The most frequent site for the referred pain was the back (fifty-one). Five patients had pain referred to the right shoulder, three had cholelithiasis and one a subdiaphragmatic abscess, which probably explains the radia-

tion Three of the eleven patients in whom the pain spread to the right upper quadrant had a pathologic condition of the gallbladder in addition to the ulcers Radiation occurred in various directions in thirty-two other cases for which no explanation other than ulcer could be found

Three hundred and eight placed the onset of their distress in definite relation to meals, and in 252 of these it occurred from one to three hours afterward There was no apparent difference in behavior between gastric and duodenal ulcers

Three hundred and eighty-five patients noted relief from pain after taking food, and 394 after taking sodium bicarbonate Forty-eight were relieved by the application of pressure or heat to the epigastrium One hundred and forty-two were relieved by vomiting, and 140 noticed some relief after belching

Why there is such a wide variance in the amount of pain which patients with peptic ulcer experience is not understood clearly There is no sex difference according to our records, which also do not disclose any association with the duration of symptoms of ulcer or the age of onset It is more probable that the emotional constitution of the person and his susceptibility to pain stimuli determine how bitterly he complains This is strikingly true in many cases, yet there are other patients who, most phlegmatic in all other respects, suffer extreme pain from the ulcers, regardless of the type Unfortunately it has been impossible to analyze our hospital cases from this standpoint

*Nausea and Vomiting*—A considerable number of patients had nausea (196) or vomiting (356) during the periods when the ulcers were giving pain In most cases the cause of these symptoms was not evident, although apparently they were due to a large retention in thirty-five cases Occasionally it seemed, in observing individual cases, that the vomiting was the result of the severity of the pain that the patient experienced, yet this could not account, at most, for more than seventy-six Riegel<sup>4</sup> described a case in which vomiting was the outstanding symptom Twenty-five cases in this series might be so classified

*Condition of the Bowels*—Constipation was a symptom in 290 patients A few were constipated only during their attacks of ulcer pain Six had diarrhea at this time, and four were troubled with alternating constipation and diarrhea Such associated disturbances of the bowels suggests that an ulcer in some instances may disturb the whole intestinal tract

*Weight*—One hundred and twenty patients of the cases in which weight was mentioned lost during their attacks of ulcer distress, the loss varying from 5 to 50 pounds (2.3 to 22.7 Kg) Only five gained weight during their illness In the other 168 cases, a change in weight did not occur

## LABORATORY DATA

White blood cell counts were made in all but fourteen cases. One hundred and sixty-eight patients had a leukocytosis (over 10,000). In twenty-five cases perforation had occurred. The condition in three cases was due to a complicating disease such as pneumonia. Sixty-six were patients who had bled and showed the mild increase associated with secondary anemia. In seventy-four cases, however, there was nothing to account for the leukocytosis. It seems important to bear this in mind, since the observation of an abnormal white count in an otherwise simple case of ulcer sometimes causes undue apprehension. Red blood cell counts, as well as the examinations of the stools, were of interest only

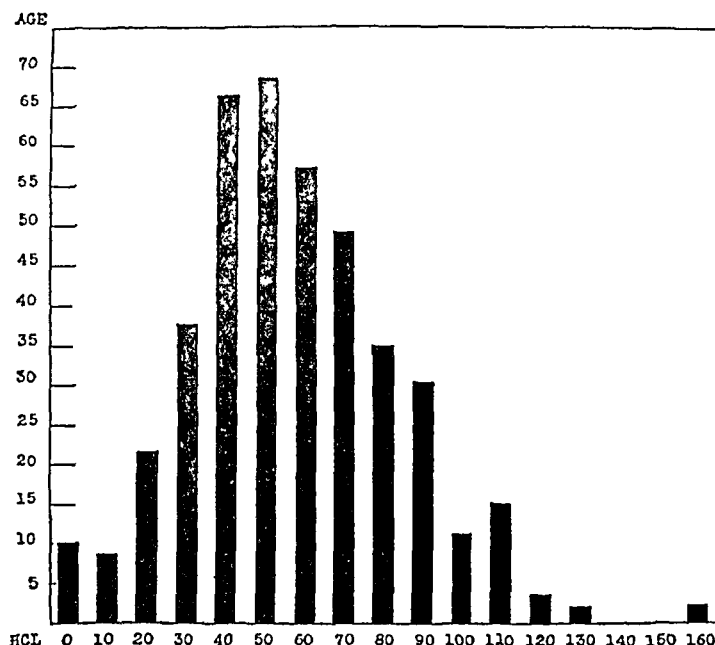


Chart 2—The highest values of free hydrochloric acid in the gastric analyses of 414 cases of peptic ulcer

in relation to hemorrhage and are taken up under that heading. The blood pressure and urine were of no significance unless they gave definite evidence of arterial or renal disease.

Gastric acidity in cases of ulcer is of interest in view of the different opinions held concerning its importance in diagnosis, the causation of pain and its effect on healing. A gastric analysis was done on 414 patients. A test meal of 60 Gm of white bread and 200 cc of water was given, and the contents removed fractionally with the Rehfuß tube, or completely at the end of an hour with the Ewald tube. The highest value of free hydrochloric acid has been recorded in terms of the number of cubic centimeters of tenth normal sodium hydroxide necessary to neutralize 100 cc of gastric contents, as shown in chart 2.

Values were recorded on patients from 0 to 150. Approximately 50 per cent of the patients had a free acidity of fifty points or more, and 25 per cent of the total had a free acidity of seventy or over. The majority of the patients, therefore, may be said to have a hyperacidity. On the other hand, one fourth of all the patients had a normal range of from twenty to forty points of free acid, and 9 per cent had twenty or less.

When the acid values vary so freely through such a wide range, the gastric analysis can be of little diagnostic value in the individual case. Moreover, the not infrequent custom of diagnosing the presence of an ulcer on the basis of an existing hyperacidity does not seem warranted when the tendency for the ulcer to occur with hyperacidity is no greater than represented by this series.

There is a wide range of opinion among writers concerning the ability of ulcers to develop and persist in the absence of free acid, and concerning the possibility of an ulcer giving typical distress of ulcer in the absence of free acid.<sup>13</sup>

An analysis of the results for ten patients who were found to have no free hydrochloric acid in their gastric contents shows that the condition in one was in association with pernicious anemia, and doubtless a true achylia gastrica. This patient had never experienced distress from ulcer, and the characteristic deformity of duodenal ulcer was discovered in a routine roentgen examination. The evidence for absence of free acid in the other cases is unconvincing. Five of them had a high combined acid. Three others showed free hydrochloric acid when they were given a large meal, or when aspiration was done during a period of distress. In the last case, only one specimen of gastric juice was obtained, and a test for pepsin was not made. There is no proof, then, that true achylia gastrica occurred in any uncomplicated case in this series.

There are no data on these patients which show the relationship of acid to pain, since special work has not been done in this connection.

The usual amount of distress caused by the ulcer was compared with the highest acid values found in the patients' routine gastric analysis. Table 2 shows that about the same proportion of patients in each acid group had severe pain, and that in general the degree of distress was not related to the degree of acidity. This is in agreement with the work of Carlson<sup>14</sup> and Bolton.<sup>2</sup> It is true that in cases in which nocturnal

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13 Eggleston (footnote 1, second reference). Bolton (footnote 2). Moynihan, B. *Brit M J* 1:221, 1923. Carlson, A. J. *Am J Physiol* 45:81, 1917. Reynolds, L., and McClure, C. W. *Motor Phenomena Occurring in Normal Stomach in Presence of Peptic Ulcer and Its Pain, as Observed Fluoroscopically*, *Arch Int Med* 29:11 (Jan) 1922.

14 Carlson (footnote 13, fourth reference).

distress occurred, the acid values were a trifle higher than for all the cases, but this was so slight as to be without significance, averaging fifty-one for all cases and fifty-five and nine-tenths for those with nocturnal distress. Pain at night in this condition, however, may be dependent on a continuous night secretion.

To what extent does the degree of acidity influence the healing of an ulcer? This answer could be reached best by following a series of cases from the onset of symptoms throughout life. Although this is rarely possible, some idea should be gained by comparing the acid values

TABLE 2—*A Comparison of the Amount of Pain with the Free Acid in the Gastric Analysis of 414 Cases of Peptic Ulcer*

Highest Values of Hydrochloric Acid in Gastric Analysis	Percentage			
	None	Slight	Moderate	Severe
0	7	26	59	8
0 - 10	0	17	61	22
11 - 20	0	40	45	15
21 - 30	0	35	50	15
31 - 40	2	18	63	17
41 - 50	7	15	67	11
51 - 60	0	16	70	14
61 - 70	3	13	63	21
71 - 80	0	19	60	21
81 - 90	8	21	50	21
91 - 100	0	41	41	18
101 - 110	0	16	68	16
110 - 120	0	0	60	40

TABLE 3—*A Comparison of the Gastric Analyses of Patients with Ulcer Having Symptoms of Less Than One Year with Patients with Ulcer Having Symptoms for Twenty Years or More*

Acid Values	Less Than 1 Year	More Than 20 Years
0 - 10	0	2
11 - 20	2	1
21 - 30	3	7
31 - 40	10	5
41 - 50	6	5
51 - 60	6	10
61 - 70	4	3
71 - 80	1	2
81 - 90	4	1
91 - 100	1	1
101 - 110	1	3

in long-standing cases of ulcer with the acidity in cases of recent origin. There were thirty-eight cases with symptoms for twenty years or more and these were compared with an equal number of cases with symptoms of less than one year (table 3). No essential difference occurred in the acidity of the two groups.

#### ROENTGEN EXAMINATIONS

X-ray studies were made in 510 cases in our series, and definite ulcers were shown in 474 (93 per cent). X-ray pictures failed to show the ulcer in thirty-six cases (7 per cent), eighteen of the latter were shown to have an ulcer at operation, six, in addition to typical symptoms



had had one or more hemorrhages, and the diagnosis in twelve was based on the history and reaction to treatment alone. Sixteen of the patients were seen before 1919, in the developmental period of the radiographic signs of ulcer, and one would expect more cases to be missed than now. In the hands of a skilled roentgenologist, a definite diagnosis of ulcer can be relied on. A negative roentgen examination with a good history is probably not of so much value, for an ulcer may be so situated that it cannot be demonstrated.

#### COMPLICATIONS

*Hemorrhage*—Riegel<sup>4</sup> reported that one third of all patients with ulcer suffer from gross hemorrhage according to the statistics of different observers and he felt that this proportion would be even higher if all the blood lost in the stools could be known. Osler and McCrae<sup>15</sup> concluded, from various authorities, that hemorrhage occurred in from 25 to 60 per cent of all cases of gastric ulcer, with an average of 28 per cent, and in about 50 per cent of the cases of duodenal ulcer. Later writers found a smaller percentage. Thus, Mayo<sup>16</sup> reported that hemorrhage occurred in 17 per cent of cases of gastric ulcer and 15 per cent of the cases of duodenal ulcer, Eggleston<sup>17</sup> reported this condition in 19 per cent of his 500 cases. Our figures correspond with those of the older observers, for 194 (34.8 per cent) patients in this series had one or more gross hemorrhages. These do not include that unknown number of patients who have doubtless lost such small amounts of blood as to escape notice and those in whom the ulcers were found to be oozing, if these were included, the percentage would be 40 or more.

The importance of this complication, both for the life of the patient and for the economic disability that it entails, has not been emphasized sufficiently in recent years. Its gravity is apparent when it is seen that eight patients died from loss of blood. This is 4.1 per cent of the cases in which hemorrhage occurred, and is 1.4 per cent of the series. Four patients died from a single hemorrhage and four after several of them.

Examination of the blood and stools showed that eighty of these patients were definitely anemic at the time of their entry into the hospital (fourteen had from 1,000,000 to 2,000,000 red blood cells per cubic millimeter, thirty-two had from 2,000,000 to 3,000,000, and thirty-four had from 3,000,000 to 4,000,000). Twenty-four patients who showed no evidence of anemia had typical tarry stools. Thirty-one others showed occult blood in the stools without anemia. The remaining fifty-nine, at one time or another during the course of their disease, had a recog-

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15 Osler, W., and McCrae, T. *System of Medicine*, ed. 1, Philadelphia, Lea & Febiger, 1908, vol. 5.

16 Mayo (footnote 1, third reference).

17 Eggleston (footnote 1, second reference).

nizable gross hemorrhage, which, on entry, did not show any effect on the blood or feces. In addition, there were sixty patients who had never had a definite hemorrhage who showed microscopic blood in the stools.

Hemorrhage was the first indication of the presence of an ulcer in twenty-five cases. Seventy-three patients had a gross loss of blood within the first two years. The time at which the other patients bled was rather evenly distributed over a period of from two to twenty-five years, eleven patients having done so after twenty years. It appeared that after a rather high incidence in the first two years, the tendency for hemorrhage to occur dropped to about 23 per cent and remained there. The number of cases is too small, however, to justify a definite conclusion.

The patient's age at the time when symptoms of ulcer first develop seems to be related to the danger of hemorrhage.

Table 4 shows a steady increase in the tendency of ulcers to bleed as they develop in patients from youth to old age. An ulcer found in

TABLE 4—*The Age of Onset of Symptoms of Ulcer as Compared with the Tendency to Hemorrhage*

Age in Decades	Number Cases with Hemorrhage	Percentage in Each Age Group of Series
10 - 20	1	1.5
21 - 30	31	22
31 - 40	60	39
41 - 50	45	41
51 - 60	39	67
61 - 70	14	63
71 - 80	4	80

a man 50 years of age should be looked on as more likely to bleed if recently acquired than if of long duration.

There was a greater proportion of males than females in the cases with hemorrhage, for 150 patients in the series were males, and forty-four were females. This is 37 per cent of the male group and 29 per cent of the female group. There was also a greater proportion of vascular disease in the cases in which hemorrhage occurred than in the whole series. Fifteen of the patients had hypertension, and seventeen had generalized arteriosclerosis. Approximately one half of the patients with a blood pressure of 160 or more have bled.

No other factors were found which were related to hemorrhage. The patient's customary degree of activity did not play any rôle. Seventy of the cases with hemorrhage occurred in persons who were in sedentary occupations, seventy-eight in those doing a moderate amount of work and forty-six in those doing strenuous physical work. The same values of free hydrochloric acid in the gastric contents occurred in these cases as in the whole group. The amount of pain experienced by these patients was not different from that in others who had not bled.

Recurring hemorrhages were frequent. Forty per cent of the patients that bled had more than one hemorrhage, and 15 per cent had "several" or "many." The patient in the most extreme case had one or more annually for twenty-five years. More than one half the patients had a second hemorrhage within a year after the first, which agrees with Riegel's<sup>4</sup> observations that a second hemorrhage usually occurs soon after the first, on the other hand, many had a second hemorrhage only after a lapse of several years.

*Perforation*—Thirty-eight patients in the series (68 per cent) suffered acute perforation of the ulcer. This is in substantial agreement with the older writers (Fenwick,<sup>18</sup> 55 per cent, Martin,<sup>3</sup> 34 per cent).

Death occurred in eleven cases, or 28 per cent, but those who recovered did not experience any ill effects as far as their general condition was concerned. Thirty-one patients were males (76 per cent) and seven females (46 per cent). Why these ulcers perforated and the others did not is no more apparent than why certain ulcers bleed.

The age of the patient at the time of onset does not bear any apparent relation to perforation. An ulcer may perforate at either extreme of life (two perforated before the patients were 20 years of age and two after the patients were 60 years of age) but usually the perforations occur during the middle period when the disease is most common.

Approximately one fourth of the patients had experienced ulcer distress for only a short time before perforation occurred. These are the dramatic cases which contribute to the idea that young ulcers are more likely to rupture than older ones. Indeed, the reverse may be true, for as Brown<sup>19</sup> has pointed out, the absence of ulcer distress before perforation does not indicate that the ulcer is acute. In our experience, the cases of perforation were divided equally between the different age groups. Most patients do, in fact, have distress for a long time before perforation occurs, eight of the thirty-eight patients had had symptoms for more than ten years.

In seven of the cases in the series there was chronic perforation of the ulcer. Four of them were gastric, one had broken through the posterior wall of the stomach and was walled off by the liver and omentum, one, on the lesser curvature, after causing an hour-glass deformity perforated into the duodenum, another, on the lesser curvature, had burrowed into the pancreas, and one had penetrated the liver. One duodenal

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18 Fenwick, S., and Fenwick, W. S. *Ulcer of the Stomach and Duodenum*, Philadelphia, P. Blakiston's Son & Company, 1900.

19 Brown, K. P. *Edinburgh M. J.* 32: 207 (April) 1925.

ulcer was completely walled off by local adhesions, another by the gall-bladder and the last had entered the pancreas and caused death by opening a large artery

*Cancer* —The incidence of ulcer as a forerunner of carcinoma is a subject of considerable discussion at present and there has been much conflicting evidence brought forward <sup>20</sup>

One hundred and twenty-nine of the 135 patients with gastric ulcer in this series have not shown any evidence of carcinoma to date. Eighty-eight of them were examined at operation or pathologically, the condition in the remainder was diagnosed only by history and roentgen observations. The average duration of symptoms was nine years, and the average follow-up in the 103 cases that were traced was four and a half years. For an average observation period of thirteen and a half years, therefore, carcinoma has not been detected in them. The remaining six cases were as follows:

One, a man, aged 51, who had been ill for one year, died of cancer of the stomach with extensive metastases one year after his hospitalization. Although the condition was diagnosed as ulcer at the time, later events make it probable that this was a case of cancer from the start. The second case was also doubtful. The patient was a woman with symptoms of ulcer extending over a period of twenty-five years, in whom the x-ray picture showed a gastric ulcer at the pylorus. Despite this fact, she was clinically thought to have cancer and, therefore, has been included at this point. Unfortunately, she refused an operation and attempts to follow her have not been successful.

A man, aged 58, who had been ill for four years, showed carcinomatous changes in the ulcer at operation, and died three years later of cancer. Similarly, a man, aged 46, who had been ill for two and a half years with a condition diagnosed as ulcer was found to have a suggestive lesion at operation, he died four months later of cancer with metastases. The fifth case was that of a woman, aged 65, who had had symptoms for ten years, and who at operation showed malignant changes in the edges of the ulcer. The last case was in a man, aged 46, with the same duration of symptoms, who at operation and by pathologic examination was reported to have a simple ulcer of the lesser curvature, yet he died of adenocarcinoma of the stomach four and a half years later without intervening relief from symptoms.

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20 Freeman, F. P., and Flinn, I. *Tr. Am. Gastro-Enterol. A.*, 1925, p. 20.  
Campo, G. *Siglo med.* 77: 193 (March) 1926.  
Stewart, M. J. *Brit. M. J.* 2: 882 (Nov.) 1925.  
Lawrence, J., and Bock, C. *Boston M. & S. J.* 195: 651, 1926.  
Wilson, L. B., and MacCarty, W. C. *Am. J. M. Sc.* 138: 846, 1909.  
MacCarty, W. C., and Broders, A. C. *Chronic Gastric Ulcer and Its Relation to Gastric Carcinoma*, *Arch. Int. Med.* 13: 208 (Feb.) 1914.

Three of the patients may not have developed the cancer from ulcer. Assuming that they did, only 4.4 per cent of the patients with gastric ulcer to date are known to have shown evidence of a malignant condition.

In none of our patients with duodenal ulcer has the condition become malignant. This is a rare event, but occasionally has been reported.<sup>21</sup>

*Retention*—In 135 cases (34 per cent) some delay was shown in the emptying time of the stomach. This was determined by roentgen examination six hours after a standard meal in 130, and clinically or by operation alone in five cases. Retention was apparently due to pyloric spasm in ninety-two. Some degree of organic obstruction was present in only forty-three cases, this was moderate in sixteen and marked in twenty-seven. In 24 per cent of the patients with duodenal ulcer, retention was produced, and in 17 per cent of those with gastric ulcer.

The development of obstruction seems to be an individual characteristic, for analysis of the cases revealed no constantly associated condition. Sex was found to be irrelevant. Eight and a half years was the average duration of symptoms of ulcer in these patients, but frequently they occurred much sooner. There was no association between obstruction and the amount of gastric acidity. The amount of pain experienced was comparable with that given by the entire group with ulcers. Thirty-eight of the forty-three patients with organic obstruction had vomited more or less frequently, but it was the outstanding symptom in only three.

The importance of retention in prognosis is hard to estimate. Patients with this symptom as a group did no better and no worse than the other patients. If retention is due to organic changes, the problem of course becomes one for surgery rather than for medicine.

*Hour-Glass Deformity*—An hour-glass deformity occurred in sixteen cases as shown by the x-ray picture. Six of these were spasmodic, no deformity being found at operation. In all except two cases the ulcers were situated on the lesser curvature of the stomach, one of these was on the posterior wall of the stomach near the lesser curvature, and the other in the duodenum with an associated contracture of the stomach. In one of the thirteen patients who came to operation the ulcer appeared to be healed. The rest showed open craters surrounded by some infiltration, and three had become adherent to the pancreas. One had formed a fistulous communication with the

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<sup>21</sup> Ewald, C. A. *Berl klin Wchnschr* **32** 527, 1886. Eichhorst, H. *Ztschr f klin Med* **14** 519, 1888. Boxwell. *Lancet* **2** 1687, 1907. Mayo, W. J. *Ulcer of the Duodenum*, *J A M A* **51** 556 (Aug 15) 1908. Letulle, M. *Bull Soc anat de Paris* **11** 741, 1897.

duodenum<sup>22</sup> Eleven occurred in females and five in males This observation agrees with the impression of others that hour-glass contraction occurs more frequently in females All these patients experienced typical symptoms of ulcer although they were complicated by symptoms of obstruction They complained of fulness or a lump after small amounts of food were taken The sensations were intense in four moderate in ten and mild in two As a result, it was sometimes difficult to obtain a good history of relief from eating

No good cause was found to explain the organic stricture One patient had syphilis, but antisyphilitic therapy had no effect on the lesion None showed malignant changes, and all have progressed fairly well Fourteen have been followed for an average of five years, none has died, and most of the patients are in good condition

#### ASSOCIATED DISEASES

*Pulmonary Tuberculosis*—Thirty patients (54 per cent) had pulmonary tuberculosis, which was considered inactive in eighteen and moderately advanced in five, it was the cause of death in one An active process did not seem to influence the course of the ulcer, nor was there any greater association of the two diseases than one would expect This disagrees with some of the older writings<sup>23</sup>

*Syphilis*—The relation of syphilis to ulcer also has been stressed during the past, but there was no greater incidence in these cases than in the general admissions to the hospital A Wassermann test was done on the blood of 433 patients and was positive in only 26 (6 per cent) Twelve of the patients had a duodenal ulcer, and five a gastric ulcer One patient had marked obstruction from a duodenal ulcer and received only antisyphilitic treatment At the end of two years all obstructive symptoms had disappeared, although typical ulcer distress was still present This is the only case in which there was clinical evidence that syphilis influenced the ulcer In addition, three of the patients were operated on, and no evidence of syphilis was found in the ulcer or stomach

*Foci of Infection*—There was no evidence that carious teeth,<sup>1</sup> diseased tonsils or sinusitis occurred more frequently in this series of cases of ulcer than should be expected in any group of persons One hundred and eighty were said to have bad teeth, forty-two had had tonsillectomies and twenty-five others had pathologic changes in the tonsils

<sup>22</sup> Monroe, R T Am J M Sc **174** 579 (Nov) 1926

<sup>23</sup> Dreschfeld, J J Allbutt and Rolleston System of Medicine, New York, The Macmillan Company, 1910, vol 3, p 446 Lisa, J R Surg Gynec Obst **41** 664 (Nov) 1925 Surmont, H Medicine **7** 772, 1926 Cade, A, and Ravault, P Am J M Sc **174** 579 (Nov) 1926

The condition of the gallbladder was noted in 228 cases, and was found to be normal when examined at operation for ulcer in 168 and by roentgen examination in twenty-nine. A diseased gallbladder was found in twenty-five cases at operation and in six, or 13 per cent, by cholecystograms.

The appendix was noted in eighty-nine cases. Thirty-five patients had had their appendix removed during an acute attack, but only twenty-five of these occurred after the onset of symptoms of ulcer. Eighteen had had appendectomies as a means of treatment for ulcers. Examination of thirty-five appendixes removed incidentally during an operation for ulcer revealed pathologic processes in only four.

#### DEATH

Seventy-six patients are dead, thirty-five died of causes not related to ulcer, twenty patients died from ulcers, if the six with gastric cancer are included, eight died of hemorrhage and six of perforation of the ulcer without operation. Twenty-one others died following an operation undertaken to cure the ulcers. This series, therefore, suffered a mortality from all causes of 13.6 per cent (or 7.2 per cent from ulcer).

#### RESULTS

The results of treatment have been observed in 460 cases which have been followed for periods varying from one half to thirteen years, the average being somewhat more than four.

Many of the patients had more than one kind of treatment (460 cases having received 562 courses of treatment), so that the average observation period for a particular form of therapy may be more or less than the general average. It is important to keep this in mind when considering results, particularly of medical as compared with surgical methods, for the average duration of follow-up in the medical cases is only two and one-half years, whereas in the cases requiring surgical measures it is slightly more than four. This difference is due to the fact that the great majority of patients who entered in the early period of the hospital's existence were operated on.

To obtain a satisfactory classification of results, a two-fold system was adopted. Depending on the evidence derived from careful questioning and examination, patients were divided into three groups, labeled "good," "improved" and "unimproved." Once the patient's group was determined, his attitude toward the treatment was classified as "satisfied" or "not satisfied."

Those were called "good" who, since treatment was concluded, have experienced no discomfort of any kind, either from the ulcer or from the treatment itself. While the latter requirement excludes a certain number that might be included by other investigators, it does not seem

logical to assert that a patient is entirely well in whom during the process of becoming so, other symptoms than the original ones have been produced. In regard to what constitutes symptoms of ulcer there is unfortunately, no complete agreement. We, therefore, have had to use our own judgment. Although a complete presentation of our views cannot be given here, it may be said that we do not agree with the idea that ulcers do not cause a specific group of symptoms. On the contrary, ulcers cause a distinct type of distress, but it may require much time and patience to separate it from other associated discomforts. A patient, therefore, having distress occurring at typical periods and relieved by food and alkali, was considered to have ulcer distress and was not classified as "good." No matter how mild this distress might be, it was sufficient to remove him from this class. In the few borderline cases, as it was known that an ulcer had been present, it seemed fairer to assume that the symptoms were due to ulcer than that they were not.

Patients in the "improved" group suffer at times from symptoms of ulcer, but, for one cause or another, are better for having been treated. In some, the symptoms are milder, in others, the remissions are definitely prolonged. In the surgical group a few patients are included in whom the obstruction has been relieved even though the symptoms are not affected, unless they are so severe as practically to incapacitate the patient. In the "unimproved" group are placed all patients who at the time of observation were obviously no better than before they underwent treatment.

After each patient had been thus classified, he was asked to express his satisfaction, or lack of it, with the results of treatment. If no definite answer was forthcoming, it was usually possible to obtain an adequate impression by his willingness to undergo similar treatment again with the hope of obtaining similar results. In the case of the few who did not return for a personal interview, it was estimated from the tone of their letters or those written by their relatives. As shown in table 5, the two forms of classification agreed extraordinarily well.

Table 5 shows the general results of treatment. There was only a little difference in the behavior of patients with gastric and those with duodenal ulcers, and, in order to simplify matters, they have been grouped together. The first column shows that as a result of treatments given to patients 37.8 per cent showed good results and the patients were satisfied, 40.6 per cent did not show any improvement and the patients were not satisfied and 21.6 per cent showed improvement. In other words, only 60 per cent were benefited by treatment of all sorts given over a thirteen year period.

In the next column are shown the results in forty-three patients in whom ulcers were not treated, and who, therefore, serve as a control.



group The reasons for lack of treatment are various, some patients refused it, some were in periods of remission, and it was not advised The follow-up record shows that untreated patients acted in general about the same as treated patients, in 23.2 per cent results were good, in 25.6 per cent improvement was shown, and in 51.1 per cent of the patients the condition was unimproved There were, thus, only 10.5 per cent fewer failures in those who were treated than in those who were not

One hundred and eighty-six patients were treated by some form of medical regimen without a previous operation In 29.8 per cent there were good results and the patients were satisfied, in 20 per cent there was improvement and the patients were satisfied, in 15 per cent there was improvement but the patients were not satisfied, and in 48.7 per cent there was no improvement and the patients were not satisfied

TABLE 5—*Results of Treatment of Patients with Ulcer*

Result	All Treatment		No Treatment		Medical* Treatment		Surgical† Treatment	
	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent
Good and satisfied	196	37.8	10	23.2	55	29.8	111	44.8
Improved and satisfied	85	16.3	11	25.6	37	20	23	9.2
Improved, not satisfied	28	5.3			4	1.5	14	5.6
Unimproved, not satisfied	210	40.6	22	51.1	90	48.7	100	40.6
Totals	519		43		186		248	

\* Medical treatment in cases not having had operation before The average observation period for medical cases was two years and five months

† Excluding cases of perforation The average observation period for surgical cases was four years and one month

Two hundred and forty-eight patients were treated by surgical measures excluding those in whom an acute perforation was present Such a condition demands emergency methods and is not strictly comparable with operations performed under more favorable conditions As a result of these measures, 44.8 per cent of the patients showed good results and were satisfied, 9.2 per cent showed improvement and were satisfied, 5.6 per cent showed improvement but were not satisfied, and 40.4 per cent did not show improvement and were not satisfied Surgical measures have given complete relief to date to more patients than medicine, 44.6 as compared with 29.8 per cent There were also fewer patients unimproved when surgical measures were used than when medicine was prescribed, 40.6 as compared with 48.7 per cent These figures, however, cannot be compared too closely As already pointed out, the average period of observation for the two methods is different The condition of the failures in the unimproved groups must also be considered

The chief reasons for failure of treatment are shown in table 6. A few more patients failed to obtain relief from pain by medical treatment than by surgical procedures. There were also more patients who bled following medical than following surgical treatment, but the difference in this regard is slight. Thus 12.9 per cent bled following treatment with medicine and 8 per cent following surgical intervention. There were eight patients receiving medical treatment who were dissatisfied with the results of treatment, although they were classified as improved. None of the patients who were improved as a result of surgical measures was dissatisfied. This seems to be largely a temperamental factor. Obstruction was as common after surgical as after

TABLE 6—Reason for Failure of Treatment

	Medical	Surgical
Pain	53	37
Hemorrhage	24	20
Obstruction	8	14
Dissatisfaction	5	
Jejunal ulcers		6
Fistulas		4
Death	3 (1.3% of all medical)	19 (6.9%, died following operation) 7 (died of ulcer later) 2 (died of secondary operation)

TABLE 7—Result of Further Treatment

	Medical Treatment after Surgical		Surgical Treatment after Medical	
	Number	Per Cent	Number	Per Cent
Good and satisfied	15	31.9	18	35.6
Improved and satisfied	16	34.0	8	15.6
Improved, not satisfied	2	4.2	3	5.8
Unimproved, not satisfied	14	30.0	22	43.1
	47		51	

medical treatment. Failures of a purely surgical nature were as follows. Six had definite jejunal ulcers and four others developed fistulas, three into the colon and one into the duodenum. Three patients who were treated with medicine died from hemorrhage, a mortality of 1.3 per cent. Twenty-eight patients who were treated surgically died: seven of ulcer at some time after discharge, two following operations performed for the repair of gastrojejunal fistulas, and nineteen as a direct result of operations for the cure of ulcer. This is a mortality of 6.9 per cent, the total number of operations performed being 275, excluding the cases in which perforation occurred and including the cases that were not followed.

Many patients who have been unimproved by one form of treatment are likely to try another form subsequently. Table 7 shows the results in this group of patients.

Fifty-one patients resorted to surgical procedures after failure of medical treatment, and forty-seven patients who had had surgical treatment took a medical regimen. Seventy per cent of those whose subsequent treatment was medical showed good results or improved, and 57 per cent of those who later chose operation showed good results or improved. Comparison of the results shown in table 7 with those in table 5 shows that medical treatment following surgical treatment gave somewhat better results than medical treatment alone. On the other hand, the results following surgical intervention in cases in which treatment with medicine was unsuccessful were not so satisfactory as in those cases in which medical treatment had not been tried. As a whole, the tables are not so dissimilar. What significance, if any, can be

TABLE 8—*Results of Various Medical Procedures*

Treatment	Number of Cases	Percentage with Good Results and Satisfied	Percentage Improved and Satisfied	Percentage Improved, Not Satisfied	Percentage Unimproved, Not Satisfied
A Gastric Ulcers					
Medical treatment undefined	3				100
Six meals and alkali	30	26.7	26.7	3.3	43.3
Sippy treatment advised	2	50.0			50.0
Sippy treatment partial	3	66.7			33.3
Sippy treatment complete	3	33.3	33.3		33.3
B Duodenal Ulcers					
Medical treatment undefined	16	25.0	18.7	6.3	50.0
Six meals and alkali	104	23.0	26.9	2.0	48.1
Sippy treatment advised	15	33.3	13.3		53.4
Sippy treatment partial	27	37.1	14.8	3.7	44.4
Sippy treatment complete	23	52.0	26.0		22.0
C Coincidental Gastric and Duodenal Ulcers					
Medical treatment undefined					
Six meals and alkali	1		100		
Sippy treatment advised	1				100.0
Sippy treatment partial	1	100.0			
Sippy treatment complete	2	100.0			

attached to these figures is not particularly evident. They suggest that a second treatment will again accomplish results similar in proportion to the first, but that the first treatment was not necessarily an unwise choice.

The results of each treatment have been tabulated in tables 8 and 9 according to the location of the ulcer. The various surgical procedures have been grouped under eight heads. Simple excision included complete removal of the ulcer, with or without cautery, and the Heineke-Mikulicz type of pyloroplasty. Gastro-enterostomy alone has been separated from other technical processes often employed with it such as plication of the pylorus, division (transection) of the pylorus, removal of the pylorus or antrum or both (the Polya or Billroth operations) and excision of the ulcer alone. The Finney type of pyloroplasty was kept distinct. Sleeve resection means the removal of a portion of the stomach with repair in continuity. Various procedures to fit the

particular cases were used in patients with acute perforations but in order to simplify analysis they have been placed in two groups with or without gastro-enterostomy. Individuality of procedure was necessarily required in the patients with chronic perforations, and these cases have not been analyzed separately. No operation for subtotal gastrectomy for ulcer was performed in this series.

Medical treatment undefined included the cases of patients who were sent home for treatment by their local physician and in whom the type

TABLE 9—*Results of Various Surgical Procedures*

Treatment	Number of Cases	Percentage with Good Results and Satisfied	Percentage Improved and Satisfied	Percentage Improved, Not Satisfied	Percentage Unimproved, Not Satisfied
A Gastric Ulcers					
Simple excision	15	67	20.0	13.3	60.0
Gastro-enterostomy	11	18.1		18.1	63.6
Gastro-enterostomy and excision	17	58.8	5.9	5.9	29.4
Gastro-enterostomy and resection of intum	6	16.7	33.3		50.0
Sleeve resection	7	43.0	28.6		28.6
Pyloroplasty (Finney)	2	50.0	50.0		
B Duodenal Ulcers					
Simple excision	13	30.7			69.3
Gastro-enterostomy	78	32.5	7.7	5.1	34.6
Gastro-enterostomy and excision	18	66.7		5.5	27.8
Gastro-enterostomy and division of pylorus	14	57.1	7.1		35.7
Gastro-enterostomy and excision of pylorus	9	44.4			55.6
Gastro-enterostomy and plication of pylorus	22	54.5	18.2		27.3
Pyloroplasty (Finney)	32	37.5	9.3	12.4	40.6
C Coincidental Gastric and Duodenal Ulcers					
Excision	2				100
Gastro-enterostomy	1				100
Gastro-enterostomy and excision	1				100
Pyloroplasty (Finney)	1				100
D Acute Perforation					
Closure and drainage	18	38.8	16.7	33.3	11.1*
Closure and gastro-enterostomy	12	41.7	25.0	25.0	8.3*
E Slow Perforations					
Various operations	9	33.3	22.2		44.4

\* Died following operation

of diet, the number of meals, the medication and the duration of treatment were all unknown.

By "6 meals and alkali," no fixed regimen is indicated. All patients who were given a rather bland diet in five or six feedings daily were included in this classification. In addition, they received varying amounts of alkali, usually consisting of from three to eight doses a day. The length of time they adhered to this schedule varied from three months to two years. Since 1924, the strict schedule of treatment as outlined by the late Dr. Sippy<sup>24</sup> has been used whenever possible.

Many of the patients fell short of these requirements, which necessitated different classifications. Those who had "Sippy advised" had the full regimen during only their four weeks' stay in the hospital and discontinued it on discharge. Those who had "Sippy partial" adhered to the treatment fairly well after discharge for a period not exceeding six months. Those who had "Sippy full" took the treatment faithfully for from six to twelve months.

It is impossible to compare the results in tables 8 and 9 too closely owing to the marked inequality in the size of the groups and the differences in the length of follow-up. It is evident, however, that patients with gastric ulcers did not do so well as those with duodenal ulcers. This is not so marked with medical treatment as with surgical. The

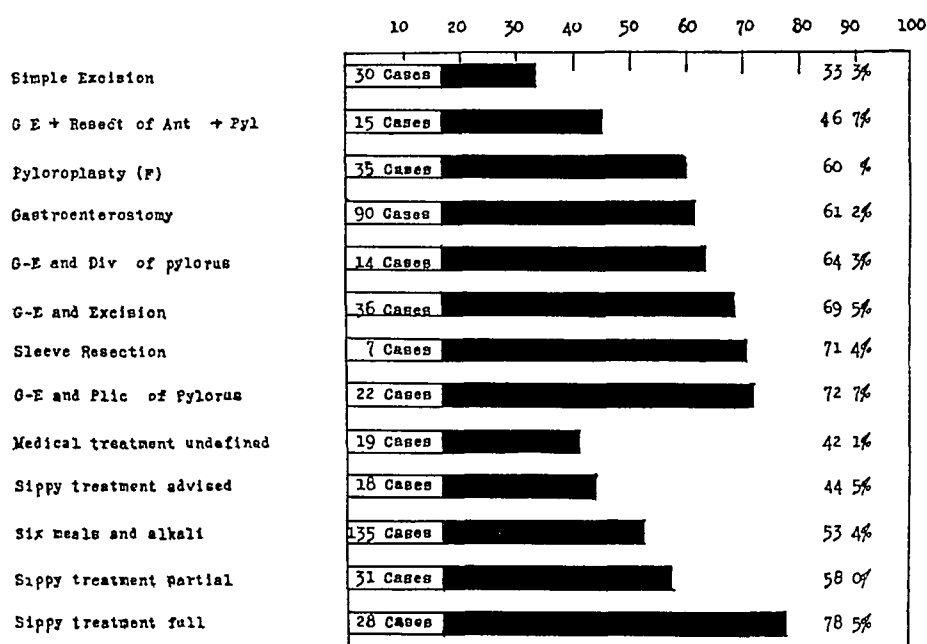


Chart 3—Results of various treatments in 249 cases of ulcer in which surgical intervention was done and in 231 cases in which medical treatment was used. The shaded areas show the percentages of good and improved cases.

different methods of treatment arrange themselves in the same order of efficiency for the gastric as for the duodenal ulcer.

The results obtained by the various therapeutic procedures are shown in chart 3 in which the shaded areas represent the good and improved cases of both gastric and duodenal ulcers. It shows that of the surgical procedures, simple excision did the least for the patients, and gastroenterostomy with plication of the pylorus did the most. Of the medical treatments, patients in the undefined group did the worst, and the patients receiving a complete Sippy regimen did the best. It must be remembered, however, that the patients receiving the Sippy treatment have been observed for the shortest period.

Surgical methods were in general more effective than medical, but these better results were somewhat offset by the more disastrous consequences in the cases in which surgical measures failed

#### COMMENT

The general result of treatment in this group of cases is apparently less satisfactory than that usually reported by others. It may not be so in reality, for similar results can be expressed differently, depending on the means of classification employed or one's point of view concerning the disease. However, one would not expect the result to be poor, since it represents the efforts of an entire hospital staff over a period of more than ten years, and the use of most of the generally accepted forms of therapy. Some forms were more effective than others, but even the best was not so good as most published claims.

For some time it has seemed to us that such claims were unsound. They are not in harmony with the number of dissatisfied patients who return each year. The warm and perennial discussion in medical literature concerning the best method of treatment is sufficient witness that this disheartening experience is by no means local. Any treatment that gives good results in from 85 to 95 per cent of cases, as is frequently asserted, is good, and far better than is available in combating many diseases.

This series of cases consisted, for the most part, of patients whom we have not seen or treated. It was, therefore, the study of a fairly representative group, concerning which predetermined conclusions have not been reached. The results seem more in accord with our ideas of peptic ulcer. The failure of most reports in the literature to agree seems to be either because they are based on an inadequate classification or because the writers fail to appreciate the chronic nature of the disease.

Some generally accepted method of classification is necessary if statistics on treatment are to be compared. This should include, first, a clear definition of the status of the patient, in terms of well recognized criteria. Typical symptoms of ulcer were used in the present study as the most reliable guide, and, as a check, the satisfaction of the patient was determined. The reasons for this have been discussed. Other methods, such as the roentgen examination, have proved singularly unreliable, and they should be used with considerable caution until more is known about them. The length of the period of observation following the completion of treatment also should be stated. This frequently is neglected. Although it was an average of four years in this series a five-year period would be much better.

The nature of the disease is such that no shorter period can be chosen safely. Whatever the cause or the nature of the remissions may

be, once an ulcer is established it is likely to persist or to recur. The average duration of symptoms of ulcer before treatment in our cases was seven years. This figure is lowered by the small group of patients who were seen shortly after onset because of perforation, hemorrhage or some such striking disability. Many had suffered for a much longer time, several for twenty years and one for forty years. Rarely were the symptoms continuous. Some had had periods of freedom for only a few months, but freedom in others lasted for years, in one for twenty years. In such a case it may be said that one ulcer healed and a new one formed. But when spontaneous remissions vary so greatly in duration, it is difficult to distinguish them from true healing. It is not justifiable to say that absence of symptoms for a few weeks or months constitutes a remission and that absence for more than a year means a cure. A person who has once had an ulcer stands a much greater chance of having the symptoms recur at some later date than if he had never had one, no matter how long he may be free from symptoms. In this sense, at least, the disease is chronic, and it makes little difference under what circumstances a remission is induced. For this reason also, a five year period of observation should be a minimum for reporting cures.

Roentgen examinations often have been sadly misinterpreted in reporting the results of treatment. Disappearance of the gastric niche following treatment has been considered strong evidence for healing, and the infrequent disappearance of the duodenal deformity has been attributed to permanent scar tissue contraction. Critical study of the x-ray observations in cases followed for a long period of time, however, strongly supports the idea that ulcer is a chronic disease. Time and again the gastric niche has been seen to smooth out under the most superficial measures, and to return promptly after the completion of even the most intensive treatments, medical or surgical. One has the impression that any therapy one may use is palliative and not curative.

The appearance of the duodenal ulcer is less easily influenced than that of the gastric ulcer, but the recent conception of the "fleck" ulcer is significant. Several of these cases have been seen at the Peter Bent Brigham Hospital. The patients have had characteristic symptoms of an active ulcer, although the duodenal caps had filled completely and well. Removal of the barium sulphate revealed typical ulcer craters. At subsequent examinations, a deformity might appear and later disappear, only to return again. Yet this defect obviously due to spasm has the same appearance as those deformities attributed to scar tissue. Of the patients in our series who had the usual deformity due to duodenal ulcer an x-ray picture had been taken in sixty-seven after treatment (both medical and surgical), and only five (or 7 per cent) have shown a return to normal. It is hard to believe that the rest

were cured, since there were persistent roentgen changes, it is easier to feel that those five will later show similar pathologic changes.

Pathologic evidence often has been presented to show that ulcers do heal, but this also may be misleading. Contemporary pathologists do not report scars of healed ulcers as frequently as the older continental workers, so they are more in accord with the clinical evidence of chronicity. The following cases are of interest in this connection.

A laborer, aged 50, came to the Brigham Outdoor Department in May, 1926, complaining of symptoms of ulcer of two year's duration. Roentgen examination revealed a characteristic niche high on the lesser curvature of the stomach. He was advised to enter the hospital for operation, which he did two weeks later. During this interval the symptoms had disappeared, and he was thought to have entered on a remission, nevertheless, an operation was performed. A small area on the lesser curvature was located with difficulty, excised in the usual manner, and the specimen sent to the pathologic department. A Cushing silver clip was then placed on the peritoneal surface of the stomach to mark the location of the ulcer. The pathologic report was that of a healing, almost healed ulcer. Despite this fact, an x-ray picture taken five days after operation revealed a defect similar to that before surgical intervention, and located in the same spot as shown by the clip. Symptoms recurred in two months, and both the symptoms and the x-ray observations have remained the same to date. In the second case, typical symptoms returned nine and a half years after excision of a gastric ulcer, and roentgen study showed the lesion in exactly the same place as before, as far as could be determined.

More observations of this kind are needed, but these are enough to throw doubt on the value of a pathologic report, as far as the cure of the disease is concerned. They suggest that the local ulcerative spot may undergo healing processes rapidly. They suggest further that remissions in the symptoms actually may be accompanied by a quiescence of the ulcerative process. We have been prone to regard the disease of ulcer as a local disorder in the gastro-intestinal tract. In reality, the evidence points to the ulceration as a local manifestation of a deep-seated disorder. This would explain the rapid return of an ulcerative condition following surgical removal of an ulcer and particularly, a return to the same site.

These considerations will be clarified only when a deeper knowledge of the disease is gained. Then, too, we shall possess a better treatment, for all of our present methods primarily relieve symptoms, except when perforation or some mechanical defect has occurred. This is evident when one compares the general result of all treatment with the results in the group to which treatment was not given (table 5). The former showed only 10 per cent more improved cases. Careful study of the other figures in the table shows that the two groups are not dissimilar.

The results of surgical treatment have been better than those of medical treatment and a study of the various operative methods used shows that the most successful were those which changed the local



condition most. This may be due to a correction of the factors that are responsible for the symptoms rather than to any curative effect on the disease itself. For example, many of our patients on whom gastroenterostomies have been performed have been entirely free from distress except during periods of unusual emotional strain (automobile accidents, death in the family, financial worries) or acute infections (colds, etc.). Others have had massive hemorrhages months and years after operation without any warning symptoms. We have been unable to escape the feeling that the disease in each instance has persisted, although the patients are, on the whole, comfortable.

We do not mean to imply that treatment has not been worth while, for much can be done for the patient with ulcer. His life may be saved in case of perforation. Obstruction can be overcome. His symptoms can be relieved, and he is enabled to lead a normal existence. It is beyond the scope of this paper to discuss the indications for the various methods of treatment. Each has its advantages and its disadvantages, and both must be carefully weighed with reference to the particular case at hand. But it is important to remember that cure cannot be promised with any of these methods. To advocate any one method in preference to all the others and to claim a high percentage of permanent relief is not justified by the results.

A patient with ulcer is notoriously of a wandering disposition. He goes from one physician to another in search of a cure. A return of symptoms leads him to consult some one else, who may understand his case better. The new advice is often different from the old, and is again accompanied by the assumption that rigid adherence to the new regimen will be followed by permanent results. This causes an unsatisfactory state of affairs. The physician is led to believe that his treatment has been efficacious, since the patient does not return. The patient loses confidence.

This situation could be much improved by a realization that patients with peptic ulcer have a truly chronic disease, not unlike diabetes mellitus or chronic nephritis, for which no cure is known. The present methods of treatment will then be used with more discretion, and the patients, being informed of their prospects, will be transformed into a cooperative group. In this way, better results will be obtained than in the past. Cure can come only when the real nature of the disease is understood, and when a method is devised which strikes at the cause and not at the symptoms.

#### SUMMARY

An analysis of 556 cases of chronic peptic ulcer seen during the years 1913 to 1926 is presented. Figures concerning the incidence, symptomatology, laboratory observations and complications are given.

Hyperacidity occurred in 50 per cent. There was only one proved case of achlorhydria, and in this the diagnosis of ulcer was made only by the x-rays, there being no symptoms of the disease.

The x-rays failed to show evidence of an ulcer in thirty-six cases (7 per cent).

Hemorrhage occurred in 194 (34.8 per cent) of the cases and was the cause of death in eight. Seventy-seven of this group had more than one hemorrhage. It was the first sign of the disease in twenty-five. After a rather high incidence in the first two years of symptoms, the proportion fell to 23 per cent and remained there.

Acute perforation occurred in thirty-eight patients, eleven of whom (28 per cent) died. There was no tendency for this complication to appear early in the course of the disease.

Cancer was found in six of the 135 cases of gastric ulcer (4.4 per cent), of these, three apparently developed from the ulcer.

Retention occurred in 135 cases, ninety-two being due to pyloric spasm.

Hour-glass deformity occurred in sixteen.

No greater incidence of foci of infection was found in this group than in the general hospital population.

Ulcer was the cause of death in forty-one cases to date; twenty-one patients died following operation.

The results of all forms of treatment showed that about 60 per cent of the patients were relieved after an average observation period of four years. The strict Sippy treatment proved to be the best of the medical methods, and gastro-enterostomy with plication of the pylorus the best of the surgical methods. Surgical measures were somewhat more effective than medical, but this was offset by the fact that the results in the cases in which surgical measures were employed were worse than the ones in which medical treatment was given.

All evidence points to the fact that ulcer is a chronic disease and that all the present methods of treatment are merely palliative. Cure probably is rare. Each method has its advantages and disadvantages, which must be weighed in the individual case. The best results are to be expected from a wise choice of these methods, the education of the patient concerning the nature of his condition and the amount of relief that can be expected.

# SOME MEDICOLEGAL ASPECTS OF OCCUPATIONAL DISEASE <sup>†</sup>

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In the past five years, New Jersey has experienced the occurrence of fatal cases of occupational poisonings in new industrial diseases or in new forms of old diseases, which has called attention to the present inadequate method of compensating workmen through a schedule of specific diseases. This list of occupational diseases in New Jersey includes anthrax, poisoning from phosphorus, benzol and its homologs, wood alcohol, lead, mercury, arsenic and chromium, caisson disease and, recently, radium necrosis.

The types of poisoning I shall discuss are tetra-ethyl lead and benzol poisoning and radium necrosis.

In 1923, two factories in New Jersey manufactured tetra-ethyl lead, a volatile liquid substance which is added to gasoline to give greater compression and hence more power to motors. The strength of this substance may be estimated from the fact that one gallon of tetra-ethyl lead is added to 5,000 gallons of gasoline to make the proper solution for high compression motors. The crude manner in which it was at first manufactured exposed workmen to its deadly effect. Of twenty-eight men directly exposed to this substance, six died from a severe form of lead encephalopathy, many of them having convulsions, four are now in asylums for the insane and sixteen have various permanent disabilities such as cranial and peripheral nerve palsies, nephritis and marked loss of weight and strength. One man has been under my care for three years. Before the onset of the lead poisoning he weighed 185 pounds (83.9 Kg.), he now weighs 125 pounds (56.7 Kg.), and has a double paralysis of the seventh and motor roots of the fifth cranial nerve. Mentally, he alternates between states of excitement and depression and is often forced to perform impulsive acts almost involuntarily. Although injury due to lead poisoning was compensable under the law of New Jersey at the time, sixteen of the persons who were affected by the poison elected to sue under the common law on the basis that tetra-ethyl lead was a new poison not listed under the compensation law. The cases were never decided by law since they were all settled out of court for large sums. At the present time, only one fac-

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<sup>~</sup> Read before the Fifth International Congress of Industrial Accidents and Occupational Disease, Budapest, Sept. 5, 1928.

tory in the country makes tetra-ethyl lead by a process which from start to finish is completely closed so that the worker is not exposed. Since the establishment of this plant, no new cases of tetra-ethyl lead poisoning have been reported.

The occurrence of thirteen fatal cases of benzol poisoning in the past year and a half has called attention to a widespread occupational hazard that may soon rival that of lead poisoning. Two of the deaths occurred in the sulphonation of benzene during the synthetic production of phenol—one of these was a watchman in the factory, and the other a helper working near one of the mixing vats. Three men, including the original cleaner and the two men who went to his rescue, died after cleaning out a single tank that had contained dump oil with benzol. All three neglected to wear masks or to carry emergency ropes. It was interesting to note the different effect of the benzol in these two instances. In the first instance, both men were found narcotized and died several hours later without gaining consciousness. In the second instance, the three men were found dead and were apparently asphyxiated almost at once, probably owing to the exclusion of air on account of the large concentration of benzol fumes. The remaining cases were those of chronic benzol poisoning occurring in three separate factories, all of which were making artificial leather by the application of a dope or mixture containing nitro-cellulose bases dissolved in a vehicle of benzol to a fabric or cloth. The latter cases occurred in men who had worked for varying periods of time, from a few weeks to several years, and who were exposed to varying concentrations of benzol fumes. They all succumbed to an aplastic leukopenic anemia, with buccal sepsis, and multiple hemorrhages from the skin and the mucous and serous membranes. Following the occurrence of these fatal cases, 110 different claims were made for compensation for alleged benzol poisoning. Since the condition can hardly be diagnosed in its early stages, the difficulty of arbitrating these cases became great.

The following postulates were taken for a standard and guide in New Jersey: 1. The claimant must demonstrate an exposure to benzol poisoning. 2. The claimant must present symptoms of benzol poisoning. 3. The claimant must demonstrate a change in his blood picture.

A tentative diagnosis of benzol poisoning was made when the claimant satisfied the first two postulates, while a positive diagnosis was made in the presence of the characteristic blood changes.

Clinically, the symptoms may be divided into three groups: (1) those due to local irritation such as conjunctivitis, bronchitis and stomatitis, (2) those due to the effects of blood disturbances or anemia such as pallor, muscular weakness, gastric disturbances, dizziness, petechial hemorrhages, purpuric spots, menstrual disturbances and occasionally cyanosis, (3) those due to nervous symptoms such as muscular tremor,

inebriation, insomnia, hallucinations and euphoria. None of these symptoms are pathognomic, although a grouping of many may lead to a diagnosis. Most reliance is placed on the blood picture which may show only a secondary leukopenic anemia in the early stages. Of 289 men examined in an artificial leather factory, 46 showed a definite secondary leukopenic anemia, some of the blood counts were as low as 2,800,000, the white cell counts as low as 3,300 and the hemoglobin contents as low as 30 per cent. When the continued effect of benzol finally paralyzes the hematopoetic centers in the bone marrow, an anemia of the aplastic or a regenerative type develops, characterized by an extremely low red and white cell count, as low as 500,000 red cells, 500 white cells and 15 per cent hemoglobin, an absence of new forms and a marked reduction of the blood platelets. As a result hemorrhages occur from the mucous membranes, usually with a fatal outcome.

The widespread use of benzol in the artificial leather industry, the rubber industry, and in the manufacture of sanitary cans, and the harmful effects of its use have caused industry in New Jersey to cooperate with the department of labor in correcting this trouble by abandoning the use of benzol and substituting for it less toxic solvents such as xylol, toluol and high flash naphtha at an only slightly increased expense. This year there were only nineteen new cases reported and two deaths listed among the thirteen referred to in the foregoing paragraphs.

In 1923, the first cases of radium poisoning were referred to the rehabilitation clinic. One woman, aged 24, had worked for seven years as a dial painter, during which time she pointed the brush she used with her lips, thereby ingesting some of the radioactive substance that had been added to the zinc sulphide paint to make it permanently luminous.

Chronic anemia with extensive necrosis of the inferior maxilla developed. Her blood picture showed profound anemia with a color index of one plus, a large cell anisocytosis with many macrocytes, a slight polychromatophilia, occasional granular basophilia and a scant number of nucleated red cells and a rare megaloblast. The blood platelets were normal, and purpura or bleeding was not elicited. The icterus index and van den Bergh tests were negative, showing that the anemia was not due to hemolysis but to a lack of production of the ordinary blood forms. After an illness of three years, she died from a progressive anemia with extensive necrosis of the lower and upper maxillae and a terminal bronchopneumonia. Autopsy, by Martland, showed intense replacement of the normal adult fatty marrow by a red, regenerating bone marrow. The organs were tested after incineration for radioactivity and showed storage of radioactivity in the bones to a large extent and to a lesser extent in the spleen and liver.

Since this case, eleven other patients who were exposed died, five others are still alive, but they are suffering from severe anemia. The absence of a provision in the Workmen's Compensation law made the latter resort to common law for redress, so settlements have been made by the company. The disease is now included in the compensation law.

In view of the limited knowledge and comparatively few cases of radium necrosis adequately studied, I have been unable to set up any diagnostic standards. However, for the purpose of guidance the following factors must be considered:

- 1 History of exposure to radioactive substances
- 2 Symptoms of anemia including the blood picture
- 3 Local symptoms of a jaw necrosis or radiation osteitis
- 4 Physical tests of radioactivity
  - (a) Autoradiography
  - (b) Electrometer test both to expired air in the living and to mineralized bone after death

These are some of the problems that the individual medical examiner or expert must meet in arbitrating claims for compensation. To recapitulate, new diseases or new disease schedules are made without acquaintance with the physiologic action of the poisons mentioned. There is a marked lack of interest and cooperation on the part of the members of the medical profession on whose reports one must often depend for important information. Many are unfamiliar with the field of industrial medicine and send clinical or laboratory reports which are inaccurate or which, having been performed too late, are useless. Through incorrect diagnoses many workmen who are suffering from occupational diseases called by other names are being deprived of their just compensation. Furthermore, there are no existing standards on which one can rely for guidance such, for example, as the definition of lead absorption and lead intoxication. The work of such committees as the South Africa Committee on Silicosis and the Standards Committee of the American Public Health Association is a step in the right direction.

# OPIUM ADDICTION

## V MISCELLANEOUS OBSERVATIONS ON HUMAN ADDICTS DURING THE ADMINISTRATION OF MORPHINE<sup>1</sup>

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AND

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In this paper we wish to present further results obtained from a study of a series of male opium addicts made while we were supplying their needs with morphine. These studies include fractional gastric analysis, roentgen examination of the gastro-intestinal tract, functional tests of the liver, dextrose tolerance tests, chemical and microscopic examinations of the urine, phenolsulphonphthalein tests and studies of the basal metabolic rate, temperature, blood sugar response to morphine and to epinephrine and the results of roentgen examination for persistent thymus.

### FRACTIONAL GASTRIC ANALYSIS

The secretory response of free and total acid of the stomach to the standard Ewald test meal was studied by the fractional method in eighteen different addicts. In all cases, samples of gastric juice during fasting were removed for analysis. Table 1 gives the results obtained in these cases for the contents both during fasting and at intervals of fifteen minutes following completion of the meal. As seen from the tables, both the free and the combined acid of the gastric juice during fasting varied considerably. An analysis of the individual cases showed that in six no free hydrochloric acid was present during the fasting stage. Four of these six cases still failed to show the presence of free hydrochloric acid fifteen minutes after the test meal was given. In one case, no free acid was found during the entire period of 105 minutes following the meal, while in two others in this group only small quantities were found. The other twelve cases presented a normal response of

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<sup>1</sup> From the Narcotic Wards of the Philadelphia General Hospital

\* Expenses of this research were defrayed by the Committee on Drug Addictions, New York City, the work was carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction, in the wards of the Philadelphia General Hospital which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia

the free hydrochloric acid when compared to the observations of Rehfuß<sup>1</sup>

All cases showed the presence of a certain amount of total acid in the gastric juice during fasting. The curves in chart 1 show the average of the total acid and free hydrochloric acid compared to the normal isotrophic curve of Rehfuß<sup>1</sup>

A comparison of these curves shows that the curves representing the total acid of the addicts are much higher while the patient is fasting than are the normal curves, while the free hydrochloric acid is always at practically the normal level. The response of the secretion of both the

TABLE 1—*The Fractional Gastric Analysis in Eighteen Cases of Opium Addiction During the Administration of Morphine*

Case No	Fasting		15 Min		30 Min		45 min		60 Min		75 Min		90 Min		105 Min	
	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total
26-1	21	34	6	24	8	32	32	59			21	40	61	86		
26-2	0	16	0	15	0	13	11	28	12	30	18	44	23	50	24	50
26-3	12	33	14	40	20	51	12	37	43	71	23	47	21	43		
26-5	19	41	34	52	58	76	42	70	52	71	21	42	7	17	7	19
26-6	6	11	7	22	21	44	28	60	56	55	37	63	40	61	40	60
26-7	11	33	8	28	16	50	13	50	27	71	29	78	32	78	32	78
26-9	0	14	0	17	5	25	0	20	0	28	11	35	29	58	27	54
26-10	31	45	10	27	7	25	4	23	2	28	0	30	0	22	0	23
26-11	13	33	0	22	4	27	12	31	41	55	40	76	45	79	46	77
26-12	0	14	0	11	0	12	0	24	0	15	0	12	0	12	0	13
26-13	0	11	4	27	22	44	30	58	48	77	31	58	28	56	39	69
26-15	0	17	0	16	4	16	18	41	25	44	23	41	13	32	0	16
26-16	0	31	0	11	0	11	0	14	4	17	5	20	3	18	0	17
26-17	28	50	55	70	45	66	43	68	37	63	40	64	41	67	42	72
26-19	25	51	16	39	12	47	19	41	20	48	21	49	25	51	24	51
26-31	10	29	8	25	20	42	50	71	57	83	59	80	16	66	24	39
26-22	47	75	47	70	52	77	53	81	48	84	57	90	60	93	60	94
26-24	24	75	18	78	41	67	50	74	38	56	13	42	11	26	16	30
Average	13.7	34.0	12.6	33.0	18.6	40.1	25.1	47.5	30.0	55.6	24.6	50.5	25.9	50.8	23.8	47.8

free and the total acids is much slower in the addict and does not reach the magnitude of the normal curve. Both, however, reach their peaks at the same time as do the normal curves and decline at the same rate. There was no correlation between the variations in the different individual responses and the amount of drug administered or the history of length of addiction.

#### ROENTGENOGRAMS OF THE GASTRO-INTESTINAL TRACT

Through the courtesy of Dr. E. Buville-Holmes, in charge of the x-ray work in the Philadelphia General Hospital, we had sixteen patients

<sup>1</sup> Rehfuß, Martin E., Bergheim, O., and Hawk, P. B. The Fractional Study of Gastric Digestion with a Description of Normal and Pathologic Curves, J. A. M. A. **63** 909 (Sept. 12) 1914.



examined after the usual barium meal in order to gather what information we could as to the movements of the stomach and the speed of passage of the barium along the gastro-intestinal tract. The results obtained showed that in the sixteen patients there was but one with definite ptosis of the stomach, this patient also showed marked atony. He also failed to show the presence of any free hydrochloric acid when subjected to the fractional test meal. Five cases exhibited hyperperistalsis and three hypoperistalsis, the peristaltic movements in the other cases being normal. Five cases showed slight atony of the muscular wall. Not any of the cases showed the presence of any organic lesion,

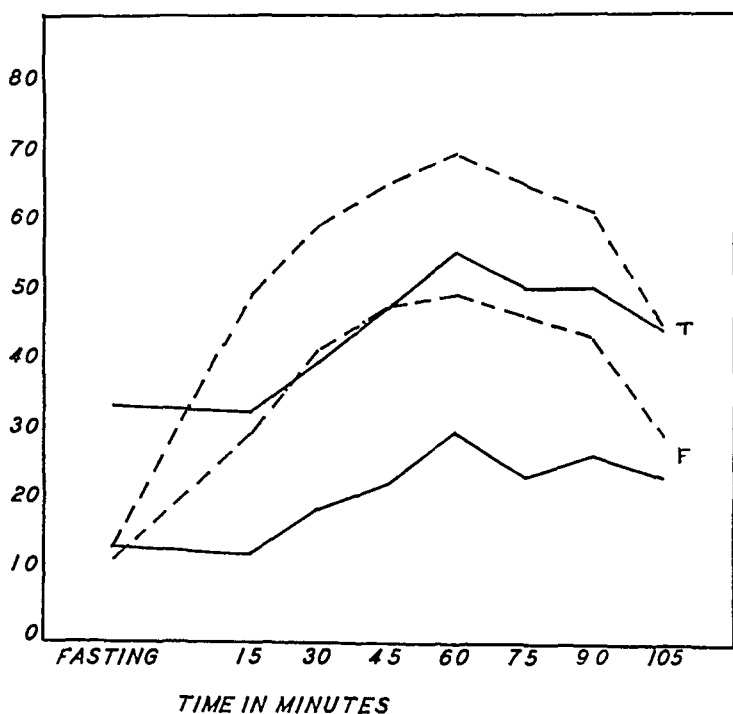


Chart 1—Average response to a standard test meal of the gastric secretion of a group of human addicts receiving morphine, compared to the normal isotrophic curve of Rehfuess. *T* indicates total acid and *F*, free hydrochloric acid. In this chart and in charts 2 and 3, the solid line indicates addicts and the broken line, normal persons.

the colon being normal and pylorospasm absent. In three cases the barium failed to reach the ileocecal valve during the six hours following the ingestion of the barium. In one of the remaining thirteen cases, the barium had reached the hepatic flexure and in two the splenic flexure, in the rest, it was found in the cecum at the end of six hours. In these studies there was again no correlation in the behavior of the gastro-intestinal tract and the length of addiction or the amount of drug used by the different patients in a twenty-four hour period.

## LIVER

The phenoltetrachlorophthalein test of the function of the liver as devised by Rosenthal<sup>2</sup> was carried out in ten different addicts. In eight of the ten, the dye disappeared from the blood stream in less than one hour, the normal time of disappearance. At the end of one hour, there was still 3 per cent left in one case, and 0.9 per cent in the other. At the end of two hours, one case still showed the presence of 1 per cent of the dye. Van den Bergh's test<sup>3</sup> was negative in nine cases studied. The icterus index of the serum showed an average of 5.2 and varied from 3 to 9 in ten cases studied. The average normal of this test as devised by Murphy<sup>4</sup> is given as from 4 to 6.

## DEXTROSE TOLERANCE TEST

Ten different addicts were selected to determine the rapidity of rise and fall of dextrose in the blood following its ingestion by mouth.

TABLE 2—Results of Phenoltetrachlorophthalein, van den Bergh, Icterus Index and Dextrose Tolerance Tests in Human Addicts During the Administration of Morphine

	Phenoltetra- chlorophthalein			Van den Bergh	Icterus Index	Dextrose Tolerance, Mg per 100 Cc of Blood			
	15 Min	1 Hour	2 Hours			Fasting	15 Min	1 Hour	2 Hours
Number of cases	10	10	10	9	10	10	10	10	10
Highest	8%	3%	1%		9	120	128	170	157
Lowest	4%	0%	0%		3	96	102	98	101
Average	5.8%	0.9%	0%	Negative	5.2	107	121	130	127

Each addict was given 175 Gm of dextrose per kilogram of body weight. The average results obtained are found in table 2 and are plotted in chart 2, which also contains a normal curve. The peak of the curve is reached at the end of an hour, and the curve is still elevated at the end of two hours as compared to the normal curve shown for and derived from normal patients in the Philadelphia General Hospital. A study of the individual cases shows a striking uniformity of the curve in all but two of the cases. In one of these, the blood sugar rose to 170 mg per hundred cubic centimeters of blood at the end of one hour, while the other reached its peak of 157 mg only at the end of two hours. One

2 Rosenthal, S. M. New Method of Testing Liver Function with Phenoltetrachlorophthalein, *J. Pharm. & Exper. Therap.* **23**: 385 (June 5) 1924.

3 Van den Bergh, quoted by McNee, J. W. Jaundice. Review of Recent Work, *Quart. J. Med.* **16**: 390 (July) 1923.

4 Murphy, William P. Biliary System Functional Tests, *Arch. Int. Med.* **37**: 797 (June) 1926.

case studied showed a decided decline in blood sugar of from 128 to 98 mg in the period of fifteen minutes and one hour after the dextrose was given. The dosage administered to these addicts ranged from 5 to 16 grains (0.32 to 1.04 Gm.) of morphine sulphate in a period of twenty-four hours with no correlation between the amount of the drug and differences in the results.

#### KIDNEY

The urines of 100 addicts were subjected to the usual chemical and microscopic examination. All specimens examined were taken from the first urine passed in the morning before breakfast. The specific gravity varied from 1.014 to 1.035, the average for the 100 cases being 1.022 with nothing significant in the color. Sugar, as determined by Benedict's method, was not found in a single case. Seventeen of the 100 cases

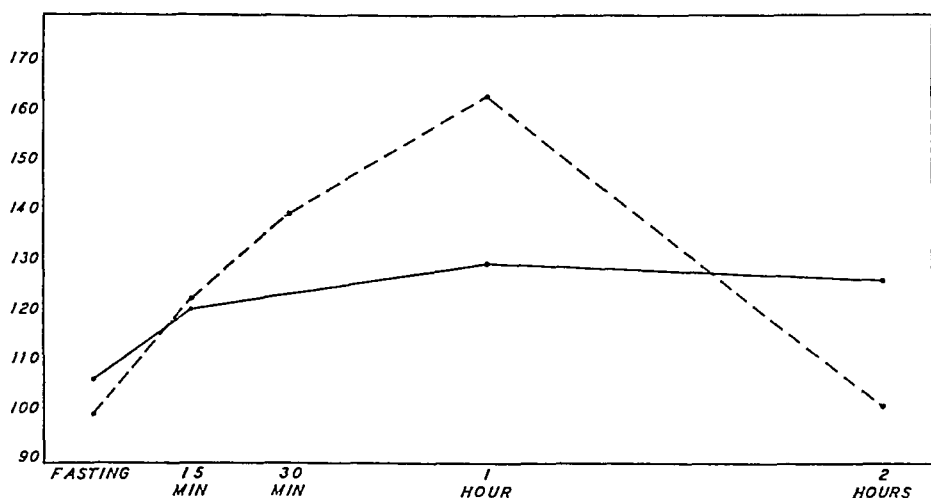


Chart 2—Average blood sugar response to the ingestion of 175 Gm. of dextrose per kilogram in a group of human addicts receiving morphine, compared to a series of normal persons.

showed from a faint trace to a trace of albumin. Of these seventeen cases, only four showed the presence of a few hyaline casts. In eighteen cases there was an excess of leukocytes, while in one case a few red blood cells were found.

The phenolsulphonphthalein test of kidney function, in which the dye was injected into the lumbar muscles, was carried out in twenty different addicts. The average elimination of the dye was 56 per cent in two hours, the average for the first hour being 42 per cent and for the second hour, 14 per cent. The lowest elimination found was 22 per cent in the first hour and 10 per cent in the second hour. The urine of this addict was free from albumin and sugar, and the blood urea nitrogen was 12 mg. per hundred cubic centimeters of blood. The most rapid elimina-

tion found was 52 per cent in the first hour and 22 per cent in the second, or a total of 74 per cent in two hours. Five of the cases showed an elimination of less than 50 per cent in two hours. All cases studied showed the greatest percentage of excretion in the first hour.

Six cases were selected and studied in which the total intake of food and water was limited to the same amount and character and given at the same period of the day. The same procedure was also carried out in three normal nonaddicts. The total quantity of urine excreted in twenty-four hours compared favorably with the total quantity excreted by the normal patients.

#### BASAL METABOLISM

Sixty-eight determinations of the basal metabolic rate were made on twenty-five different addicts. A number of additional determinations

TABLE 3—*Basal Metabolic Rate of Twenty-Five Addicts Grouped According to the Amount of Morphine Used Per Twenty-Four Hours*

	Amount of Drug Used in 24 Hours				
	0 to 4 Grains	5 to 9 Grains	10 to 14 Grains	15 to 19 Grains	20 to 24 Grains
Basal metabolic results	18 to 33	-14 to 10	-7 to 12	-5 to -16	-10 to -13
	-14 to 4	-3 to -22	9 to 15	3 to 6	-14 to -25
		-11 to 16	-12 to -28	-15 to 9	
		-13 to 2	-1 to 11	5 to 8	
		8	9 to -26	14	
			-6 to 8		
			13 to 6		
			24		
			20		
			4		
			5		

had to be discarded on account of obvious poor cooperation on the part of the patient. Prof. August Krogh's basal metabolism recording apparatus was used for this work. The accuracy of this apparatus was checked several times a week with a person whose metabolism was known to be normal. The number of determinations accepted for each person varied from a single determination to as high as four in several cases. The majority, however, were always studied until at least two determinations were obtained on separate days. The oxygen consumption was studied over a period of ten minute intervals.

Table 3 has been arranged in order to show the variations of the metabolism according to the amount of drug used in a twenty-four hour period. It will be noted that with the exception of the persons using more than 20 grains (1.3 Gm.) in a twenty-four hour period and the two using less than 4 grains (0.26 Gm.) in the same period, the extremes obtained above and below normal are practically the same, namely, -28 per cent and +24 per cent. Both persons using more than 20 grains of

morphine a day showed decreases in the basal metabolism ranging from — 10 per cent to — 13 per cent and — 14 per cent to — 25 per cent, respectively. One of the patients using only 4 grains daily had the greatest increase, namely, + 33 per cent. The cooperation at both extremes seemed to be excellent, yet we are inclined to the belief that when large quantities of the drug were used, there was considerably less nervousness than in the case in which only 4 grains were used in the twenty-four hour period.

The average variation of the entire group of sixty-eight determinations ranged from — 12 per cent to + 11 per cent, which compares favorably with the normal variation of from — 10 per cent to + 10 per cent. Thirteen of the thirty-nine results obtained in which the metabolism was found to be decreased were lower than the average low of — 12 per cent, and fourteen of the twenty-nine results obtained in which the figures ranged in the positive direction were above 12 per cent.

#### TEMPERATURE

The average temperature taken with the thermometer in the closed mouth underneath the tongue in 100 cases was found to be 98.3 F. The highest temperature reported was 98.9 and the lowest, 97.8. The rectal temperature taken in ten cases varied from 98 to 99.6 with an average of 99.2. All patients selected were free from abscesses and intercurrent infection.

#### THE EFFECT OF A SINGLE DOSE OF MORPHINE ON THE BLOOD SUGAR OF THE ADDICT

Six addicts were selected from whom blood was drawn in the morning prior to the time at which the first regular injection of morphine was

TABLE 4—*Average Response of the Blood Sugar in Human Addicts to a Single Dose of Morphine*

Number of Cases	Basal	After Injection				
		15 Minutes	30 Minutes	1 Hour	1½ Hours	2 Hours
6	84 mg *	89 mg	93 mg	92 mg	95 mg	93 mg

\* Milligrams per hundred cubic centimeters of blood

due. They were then given their regular dosages, and samples of blood were taken at intervals of fifteen minutes, thirty minutes, one hour, one and a half hours and two hours following the injection. The samples of blood were analyzed for sugar content. Table 4 gives the average results obtained, showing the effects to be negligible, the slight rise present being within the limit of error of the method used<sup>5</sup> for analysis. Two additional

5 Folin Otto and Wu, Hsien. A Simplified and Improved Method for Determination of Sugar, J Biol Chem 41: 367 (March) 1920.

cases were selected and the same procedure followed except that the dosage given was double the amount that would have been given ordinarily. The results obtained in these two cases were identical with those obtained in the six cases in which the normal dosage was given, namely, an insignificant rise in the quantity of sugar present in the circulating blood.

#### THE EFFECT OF EPINEPHRINE ON THE BLOOD SUGAR OF ADDICTS COMPARED TO ITS EFFECT ON THAT OF NORMAL PERSONS

Five addicts were selected in order to determine the degree of response in the rise of the blood sugar to a standard injection of

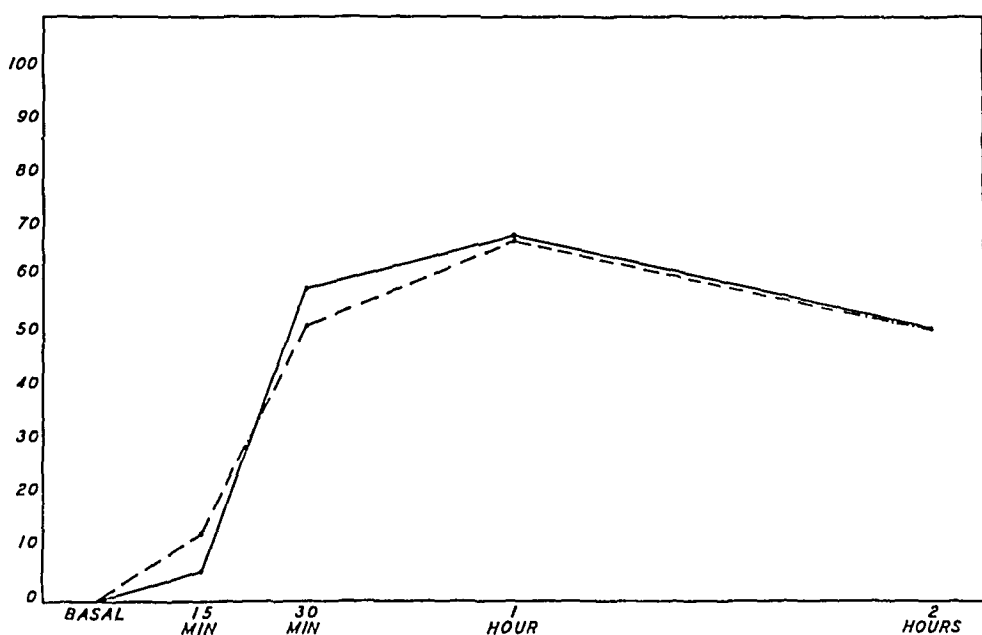


Chart 3—Average blood sugar response to the injection of 1 cc of epinephrine hydrochloride (1:1,000) in a series of human opium addicts receiving morphine, and in a group of normal persons

epinephrine, namely, 0.001 Gm of epinephrine hydrochloride. In order to obtain a comparison, the same solution was used in five normal persons.

Chart 3 shows a comparison of the relative rise of the blood sugar taken at fifteen minute, thirty minute, one hour, and two hour intervals. It will be noticed that the curves are practically identical, showing no difference in the response of the rise in sugar in addicts as compared to that of normal persons. The epinephrine was always given at an interval of fifteen minutes following the injection of the regular dosage of morphine sulphate. We have shown in the preceding paragraph that morphine per se does not cause a rise in blood sugar. The effect of the

epinephrine on the blood pressure of both addicts and normal persons was measured, but wide fluctuations in both groups did not justify the drawing of any conclusions

#### THYMUS

Roentgen studies to detect the presence of persistent thymus were made on ten addicts. The results in all cases studied were negative. From the clinical evidence there was no reason to suspect the presence of the thymus in any of our cases.

#### COMMENT AND LITERATURE

The results obtained in our studies of the stomach by means of the x-ray and fractional analysis of the gastric juice indicate little change in the behavior of this organ as the result of prolonged usage of opium or its derivatives. Sollier<sup>6</sup> asserted that not only does morphine stimulate the function of the gastric glands, but it also increases the tonicity of the stomach, and that as soon as the drug is withdrawn the stomach dilates. Morat<sup>7</sup> called attention to the markedly affected condition of the digestive tract, pointing out that the salivary secretion was much lessened and that the gastric and intestinal glands suffered no less. Bishop<sup>8</sup> described the impaired digestion of addicts. The degree of atony present in four of our five cases was so slight as to demand little attention, so that only one of our sixteen cases showed any marked change in the muscular tone of the stomach. The same comment may be made concerning the peristaltic movements, in five cases a degree of hyperperistalsis and in three cases hypoperistalsis were present.

We do not believe that the secretion of the gastric juice is impaired to any great extent. There was a delay in four of the eighteen cases studied, and the average total response was less than the isotrophic response of Rehfuess<sup>1</sup>. Thirteen of our cases showed a normal response, the quantity secreted being well within the normal limits.

The rate of progression of the barium through the small intestine was decreased in three cases. This delay in movement is undoubtedly significant and may perhaps be attributed to the action of the drug, but it is not universally present, as in the other sixteen cases the movement of the barium was normal.

In 100 per cent of our cases in the ward daily evacuation of the bowels did not occur without the aid of a cathartic. This marked con-

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6 Sollier, P. La demorphinisation et le traitement rationel de la morphinomanie, *Semaine med*, 1894, pp 146-152

7 Morat, D. Le sang et les secretions au cours de la morphinomanie et de la desintoxication, Paris G. Steinheil, 1911, p 180

8 Bishop, E. S. Narcotic Drug Problem, Pathology, Pathognosis and Treatment, Philadelphia, F. A. Davis and Company, 1913, p 524

stipation is one of the few universally accepted characteristics of the behavior of the gastro-intestinal tract of addicts. We have had statements from addicts that their bowels move each day without the aid of cathartics or enemas, but in practically every case the movement was brought about because the addict refrained from the drug until a movement occurred. While the drug is being administered in the ward, we have always been forced to give relief in the form of medication or enemas.

The only manifestation that may be regarded as abnormal which we have been able to detect in the behavior of the kidney is that in seventeen of the 100 cases studied an amount of albumin ranging from a faint trace to a trace was found. Only four of these cases showed a few hyaline casts. This is in partial agreement with Levinstein<sup>9</sup> and Sollier,<sup>6</sup> who asserted that albuminuria was frequently present in opium addicts. Morat,<sup>7</sup> however, came to the conclusion that it was a common error to regard albuminuria as being present in morphinism. The impairment of the phenolsulphonphthalein excretion in only one case and possibly slight impairment in four cases does not point to serious impairment of the kidneys as ascertained by means of this test. Studies of water balance<sup>10</sup> convinced us that the amount of urine secreted by the kidneys of addicts compares favorably with that of normal persons, and we do not agree with Lambert<sup>11</sup> that the quantity of urine secreted becomes diminished after prolonged addiction. Addicts will perspire freely when using more or less than the necessary amount of the drug to prevent withdrawal symptoms, but when the drug is administered as we employed it in our water balance experiments, the ratio of fluid secreted by the kidney to the insensible loss is the same as in a normal person. The absence of the dextrose is in agreement with the normal blood sugar content and also rules out renal glycosuria.

Impairment of liver function in the addict is also practically negligible as measured by the phenoltetrachlorophthalein test of Rosenthal<sup>2</sup> as well as by the negative results of the icterus index and van den Bergh tests. Bell<sup>12</sup> claimed the presence of fatty degeneration of the liver, and Morat<sup>7</sup> and Sollier<sup>6</sup> often found tenderness over the liver and in many cases increase in its size. In addition to the results obtained

9 Levinstein, E. *Die Morphiumsucht*, translated by Charles Harrer, 1878.

10 Light, Arthur B., and Torrance, Edward G. *Opium Addiction IX Water Balance Studies During the Administration and Withdrawal of Morphine*, Arch. Int. Med., to be published.

11 Lambert, A. Chapter in Osler and McCrae. *Modern Medicine*. Philadelphia, W. B. Saunders Company, 1914.

12 Bell, F. McKee. *Morphinism and Morphinomania*, New York M. J. 93 680 1911.



by tests, we have shown that the liver in the addict still responds with a degree of glycogenolysis following the injection of epinephrine hydrochloride quite comparable to that in normal persons. The rate of both rise and fall of the blood sugar in the dextrose tolerance test is somewhat delayed and is of sufficient interest to commend further study. The injection of morphine per se does not bring about any rise in the blood sugar in addicts and is in agreement with the observations of Plant and Pierce,<sup>13</sup> who found that when addiction became established in dogs the ability of a single dose of morphine to bring about a response in blood sugar disappeared.

Conclusions as to the basal metabolism in opium addicts during the administration of a sufficient amount of the drug to supply their needs is rather difficult in view of our observations. The average of the sixty-three determinations on twenty-five different addicts falls within the normal range. Yet there are many individual determinations that will range above or below the high and low normal figures. Unfortunately, we have only two cases in which the amount of drugs taken during twenty-four hours was below 4 grains and only two in which the amount is more than 20 grains, while most of our determinations were made on addicts who needed between 5 and 20 grains a day. The cases in which both limits of dosage per day were given would suggest that using small dosages did not decrease the metabolism and, if anything, increased it, while the cases in which the large dosage was given exhibited a decrease in the metabolism. Undoubtedly we were dealing again with one of the most difficult phases of the problem of drug addiction, namely, the quantity required to prevent withdrawal symptoms and arrest the "nervousness" of which these unfortunate people complain and which we are not able to measure. We are quite certain from our experience that an additional amount of the drug beyond a certain required dosage brings about a state of both mental and physical relaxation which undoubtedly will bring metabolism to its basal level and perhaps lower. If, on the other hand, the quantity is insufficient even though the patient may relax and remain quiet during the actual determination, the emotional disturbances which these people undoubtedly have may increase the metabolic rate above the normal level. There was no correlation between the basal pulse rates and the level of the metabolic rate.

#### CONCLUSIONS

Studies of the stomach, kidney, liver, basal metabolism, thymus temperature, dextrose response to epinephrine and dextrose response to

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13 Plant, O. H., and Pierce, I. H. Studies in Chronic Morphine Poisoning in Dogs. III. The Blood Sugar During Tolerance and Withdrawal, *J. Pharm. & Exper. Therap.* **33** 371 (July) 1928.

morphine revealed no fundamental differences from normal in addicts to whom morphine was administered to supply their needs, except a slight delay in the average response of gastric secretion to a test meal, the presence of albumin in the urine in 17 per cent of the cases and wide fluctuations of the individual determinations of basal metabolism, although the average metabolic rate was within normal limits. A delay in the return of the blood sugar to normal following the ingestion of dextrose given by mouth was also noted.

## Book Reviews

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THE FUEL OF LIFE    EXPERIMENTAL STUDIES IN NORMAL AND DIABETIC ANIMALS    By JOHN JAMES RICKARD MACLEOD, M D, LL D, D Sc, F R S, Professor of Physiology, University of Toronto, Canada    Louis Clark Vanuxem Foundation    Lectures delivered at Princeton University in March, 1928    Price, \$2.50    Pp 147    Princeton, N J    Princeton University Press, 1928

This series of four lectures represents a vigorous, healthy protest against some of the orthodox views on metabolism—always a good sign in science as well as in other fields. Macleod and his school aim particularly to show the possibility of the formation of dextrose from fatty acids, and if they do not prove their point of view conclusively, they display ingenuity in, and diversity of, experimentation and a keenly critical analysis of the work of others as well as their own.

In the first lecture the chemistry of muscular contraction is thoroughly reviewed. The many loopholes possible in the determination of the respiratory quotient are honestly presented so that one feels that the scientific literature would be far better off if all those dealing with respiratory quotients would familiarize themselves with this chapter. One of the important conclusions, based on experiments on depancreatized and hepatectomized animals, is that the respiratory quotient affords no evidence that the tissues of these diabetic animals have any lessened ability to oxidize carbohydrate.

In the second chapter is discussed the manifold relationship between liver glycogen, blood sugar and muscle glycogen. Liver glycogen must be formed to supply the other two products, as shown by experiments on insulin hypoglycemia. An illuminating discussion of the G/N ratio and the demonstration that the hitherto accepted values of 2.8 and 3.65 are too low form an interesting answer to the question of the origin of blood sugar in the absence of liver glycogen, for example, in complete pancreatic diabetes. According to the author, one can account for the high G/N ratio only on the assumption of the formation of considerable dextrose from fatty acid.

The respiratory quotient in muscular exercise, starvation or in one-sided feeding with fat, protein or carbohydrate, and after pancreatectomy, forms the material of the third lecture. In spite of the low respiratory quotient in fasting diabetic animals, exercise in the form of shivering can definitely raise it almost as much as in normal animals. In connection with human and phlorizin diabetes, the work of the Lusk school particularly is analyzed, criticized and ultimately lined up in favor of Macleod's theory of the formation of dextrose from fatty acid. Direct proof of the latter seems to be available in the experiments on depancreatized dogs given injections of epinephrine, when much more dextrose was excreted under well controlled conditions than could possibly be accounted for by the prevailing nitrogen metabolism, the breakdown of all the glycogen in the liver and muscles, and the dextrose derivable from glycerol.

The last lecture deals with some of the possible intermediary products of carbohydrate metabolism, such as acetaldehyde, dihydroxyacetone, fructose and methylglyoxal. Of these, the most interesting to clinicians is dihydroxyacetone which has been widely heralded as a substitute for dextrose in the diabetes of human beings. The evidence presented in this chapter clearly dispels any such illusions and shows that, like so many other carbohydrates, dihydroxyacetone is first converted into dextrose and utilized neither more nor less than the latter in animals with diabetes.

This volume has its chief value as a logical critique of much of the prevailing work on carbohydrate metabolism, especially since it comes from the hands of one who is himself one of the masters in that branch of science. It is made attractive reading by its clear style, beautiful type, excellent detailed table of contents and exhaustive modern bibliography, not to speak of the short but com-

plete index. It is to be highly recommended to both clinicians and laboratory men as a source of information and logical reasoning.

**THYROXINE** By EDWARD C KENDALL, M S, PH D, D Sc, The Mayo Foundation, Rochester, Minn. Price, \$5.50. Pp 265, with an index and a bibliography of 541 titles. New York: The Chemical Catalog Company, 1929.

This is a useful monograph on the physiology and pathology of the thyroid gland with particular emphasis on the history of the chemical isolation of the active thyroid hormone, thyroxine. The emphasis on the chemical phase comes naturally from the author, Dr E C Kendall, who has done valuable work on the isolation of the hormone. The long list of references will be useful to physicians and investigators who want to go more deeply into the controversial phases of the problem of the thyroid gland than Dr Kendall has done in the present work. The book is clearly written and is therefore easy reading. Here and there the author goes far afield in speculation, but usually he indicates to the reader that he is on speculative ground. Dr Kendall states that "thyroxine bridges the gap between living protoplasm and the expression of what may be called personality or temperament. Thyroxine has a definite place in the study of normal and abnormal mental processes." The phenomena usually designated by the terms personality or temperament are not as yet clearly enough defined to be treated profitably in a biochemical monograph. The author further states that "the theoretical deductions in this monograph have been largely based on three contributions: the clinical classification of the goiter and the use of iodine in exophthalmic goiter by Plummer, the isolation of thyroxine, and the extensive studies on basal metabolism in relation to thyroxine and thyroid diseases as carried out by Boothby and his co-workers." In other words, the theoretical deductions reflect largely on the views and practices in the field of study of the thyroid gland represented by the Mayo Clinic. Important as the contributions to physiology, biochemistry, pathology and therapy from the Mayo Clinic are, these by no means constitute the whole story of functions and malfunctions of the thyroid gland as known today. It is useful, however, to have the standpoint of the Mayo Clinic clearly and concisely in one monograph.

**CLINICAL ASPECTS OF THE ELECTROCARDIOGRAPH** By HAROLD E B PARDEE. Second edition. Price, \$5.50. Pp 242. New York: Paul B Hoeber, 1928.

This edition of Dr Pardee's book contains revisions and additions which bring the subject matter up to date. It is written in the same clear style which characterized his first edition and which makes it one of the most readable books on the subject in English. If there is any unfavorable criticism, it lies in the author's tendency to be, perhaps, too dogmatic about some of the alterations in the cardiograph curves under pathologic conditions. These assertions are rare, however, and are perhaps warranted on the basis of clarity for the average user of the book. As the author has intimated, the increasing availability of cardiograph records and knowledge concerning them make just such a book as this worth while for the library of any internist or general practitioner.

**WHAT YOU SHOULD KNOW ABOUT HEART DISEASE** By HAROLD E B PARDEE. Price, \$1.50. Pp 120. Philadelphia: Lea & Febiger, 1928.

This is a little manual developed along the lines of some of the manuals for diabetic patients except that it is meant for persons interested in heart disease as well as for cardiac patients. As to the advisability of having such a work available there can be little doubt, and this one meets the need so adequately that even though readable by lay persons it could well serve beginning students in medicine for whom it was not primarily intended. Obviously, it should be used in "selected cases" only when the danger of adding a cardiac neurosis to an existing organic circulatory disease is not present. It is a surprisingly complete manual for its size. Many practitioners should welcome it.

BRONCHIAL ASTHMA—ITS DIAGNOSIS AND TREATMENT By HARRY L ALEXANDER Price, \$2.25 Pp 171 Philadelphia Lea & Febiger, 1928

The purpose of this book is to present an outline of bronchial asthma. The bibliography correlates the older work with the new, and in this way brings many of the early important studies to the attention of the reader. The factors which underlie an asthmatic paroxysm, the anatomic structures which participate in an attack, the fundamental questions of etiology and the treatment of the disease are well discussed. The chapter on treatment takes up all the modern methods of therapy in a concise manner, and the references are sufficient to allow a detailed study if desired. The book is well written.

# INDEX TO VOLUME 43

	PAGE		PAGE
Abscess aspiratory, of lung, pathogenesis of, its possible relation to abscess of lung following tonsillectomy	767	Blood—Continued	
Acromegaly, insulin in acromegalic diabetes	785	pressure, gallop rhythm in hypertension	166
Adrenals See Suprarenals		pressure, variability of, morning and evening studies	835
Albuminuria, in mechanism of detoxification	139	sugar, reducing power of filtrates from blood of rabbits	393
Alkalosis, chloride metabolism and, in alkali treatment of peptic ulcer	615	white cells, normal rhythm of, in women	68
occurring in anemia (probably pernicious), report and comment on case	504		
Allergy role of, in tuberculosis	691	Book Reviews	
Alt, E L Metabolism in pernicious anemia	488	A History of Pathology, E R Long	731
Andrés, A Albuminuria in mechanism of detoxification	139	A Textbook of Actinotherapy, D D Rosenwarne	144
Anemia pernicious, metabolism in (probably pernicious), alkalosis occurring in, report and comment on case	504	A Text-Book of Infectious Diseases, Goodall and Washbourn	145
Aneurysm of coronary arteries	1	Asthma Its Diagnosis and Treatment, W S Thomas	570
Angia, agranulocytic, identity of so-called	533	Bidrag Til Studiet af Asthma Særlig hos børn, K Baagoe	146
Aorta, coarctation of, case of adult type in child 6 months of age	420	Book of Diets of the McGuire Clinic and St Luke's Hospital, Department of Dietetics, Richmond, Va Pp 50 1928	570
Arrhythmia, allied, auricular fibrillation and, pathologic changes in	808	Bronchial Asthma—Its Diagnosis and Treatment, H L Alexander	892
auricular fibrillation, results of 7 years experience with quinidine sulphate therapy (1921 to 1928)	653	Clinical Aspects of the Electrocardiograph, H E B Pardee	891
Arteries, coronary, aneurysm of	1	Clinical Medicine, O W Rethea	428
Arthritis, chronic infectious bacteriology of blood and joints in	571	Clinical Studies on Infections of the Urinary Passages in Children (Danish), A Johannessen	145
Asthma, associated with colds, preventive treatment with vaccines	429	Contributory to the Study of Asthma Especially in Children (Danish), K Baagoe	146
Auricular Fibrillation See Arrhythmia		Criteria for the Classification and Diagnosis of Heart Disease, J H Bainton, W C Munly, R L Levy and H E B Pardee	426
Bachmann, H A Clinical types of edema in heart failure of childhood	795	Cushny's Pharmacology and Therapeutics, C W Edmunds	297
Bacteria, cultural and serologic reactions with green producing micrococci from measles	274	Diseases of Gall Bladder and Bile Ducts, E A Graham	568
Bergén, J A Perforations of colon in chronic ulcerative colitis	483	Epilepsy, W G Lennox	297
Specific serum treatment in chronic ulcerative colitis	50	Fungi and Fungous Diseases, A Castellan	569
Biliary Tract, humoroneural regulation of gastric, pancreatic and biliary secretions	446	Kliniske Studier Over Urinvejsinfektioner hos børn, A Johannessen	146
Blood, and joints, bacteriology of, in chronic infectious arthritis	571	Laboratory Diagnosis and Experimental Methods in Tuberculosis, H S Willis	426
cutaneous and venous, sugar curves, in benign glycosuria and in diabetes	633	Laboratory Manual of the Massachusetts General Hospital, R R Wheeler and F T Hunter	570
lipids, character of, in hepatic disorders including migraine	715	Lehrbuch der Blutkrankheiten für Ärzte und Studierende, H Hirschfeld	425
normal determinations of, in the South	96	Medicine Monographs, Volume XIV Epilepsy, W G Lennox	295
plasma, cholesterol content of, in juvenile diabetes, a statistical study	372	Metabolisme cellulaire et Metabolisme des Tumeurs, O Warburg	297
plasma, cholesterol content of, in diabetes mellitus, statistical study based on 2 000 observations in 385 cases	363	Modern Medicine Its Theory and Practice Volume VI Diseases of the Nervous Systems, and Diseases and Abnormalities of the Mind, W Osler	296

# INDEX TO VOLUME 43

Book Reviews—Continued	PAGE		PAGE
Monographien aus dem Gesamtgebiet der Physiologie der Pflanzen und der Tiere, M Gildemeister, R Goldschmidt, C Neuberg J Parnas, W Ruhland	732	Collins, L H, Jr Chronic pulmonary infection due to the Friedländer bacillus, a clinical and roentgenologic study	351
Nurses, Patients and Pocketbooks A Report of the Study of the Economics of Nursing Conducted by the Committee on the Grading of Nursing Schools, M A Burgess, Directress	144	Davis, J S, Jr Alkalosis occurring in anemia (probably pernicious), report and comment on case	504
Praktische Differential diagnostik Band 1 Teil 4 Erkrankungen der verdauungsorgane, L R Grote	732	Dextrose, tolerance, cutaneous and venous blood sugar curves in benign glycosuria and in diabetes	633
Psychoneurosen Funktionelle Neurosen Erschöpfungszustände, W Unger	146	Diabetes acromegalic, insulin in	785
Rene Theophile Hyacinthe Laenec A Memoir	732	mellitus, cholesterol content of blood plasma in, statistical study based on 2 000 observations in 385 cases	363
Special Cytology, Edited by E V Cowdry	145	mellitus, cutaneous and venous blood sugar curves in benign glycosuria and in	633
Syphilis A Treatise on Etiology Pathology Symptomatology Diagnosis Prophylaxis and Treatment, H H Hazen	296	mellitus, effect of synthalin on respiratory quotient of the diabetic patient	384
Systemic Infections Their Diagnosis and Treatment, A K Gordon	146	mellitus juvenile cholesterol content of blood plasma in	372
The Duodenum Medical Radiologic and Surgical Studies, P Duval, J C Rioux and H Beclere	427	mellitus study of 147 autopsies	377
The Examination of Patients, N B Foster	298	Diaphragm relation of hiatus esophageus of to stomach	61
The Fuel of Life Experimental Studies in Normal and Diabetic Animals, J J R Macleod	890	Diazo Reaction Andrewes in nephritis	472
The Opium Problem, C E Terry and M Pellens	427	Diehl H S The variability of blood pressure, morning and evening studies	835
Thyroxine, E C Kendall	891	Digitals effect of on the electrocardiogram, an experimental study on dogs and cats	676
Trabajos y Publicaciones de la Clinica, P Escudero	569	Eastland, J S The Andrewes Diazo reaction in nephritis	472
Ueber das Problem der Bosartigen Geschwulste eine experimentelle und theoretische Untersuchung L Heidenham	295	Edema clinical types of, in heart failure in childhood	795
What you should know about Heart Disease, H E B Pardee	891	Electrocardiogram, effect of digitals on, an experimental study on dogs and cats	676
Brams W A Effect of digitals on the electrocardiogram in experimental study on dogs and cats	676	human, changes in T wave of following iodine medication and thyroidectomy	35
Bry H A Excursion of costal margins in health and in disease	187	the discordant	549
Cancer bronchogenic squamous cell, report of case associated with pleural effusion and pulmonary osteo-arthritis with features that simulated infection by endameba histolytica	516	ventricular, an experimental study	335
Cecil R L Bacteriology of blood and joints in chronic infectious arthritis	571	Emery, E S, Jr Peptic ulcer, a study of 556 cases	846
Chloride metabolism and alkalosis in alkali treatment of peptic ulcer	614	Endameba See Entameba	
Cholesterol content of blood plasma in diabetes mellitus statistical study based on 2 000 observations in 385 cases	363	Entameba histolytica, bronchobenic squamous cell carcinoma associated with pleural effusion and pulmonary osteo-arthritis with features that simulated infection by	516
content of blood plasma in juvenile diabetes, a statistical study	372	Esler, J W Clinical significance of premature beats with particular reference to heart rate	606
Colds See Respiratory Tract		Fat metabolism studies in, character of blood lipids in hepatic disorders including migraine	715
Colitis ulcerative perforations of colon in chronic	483	Ferry N S Cultural and serologic reactions with green producing micrococci from mersles	274
ulcerative specific serum treatment in	50	Friedenson, M Cutaneous and venous blood sugar curves in benign glycosuria and in diabetes	633
		Friedlander Bacillus See Pneumonia	
		Frissell L F Alkalosis occurring in anemia (probably pernicious), report and comment on case	504

# INDEX TO VOLUME 43

	PAGE		PAGE			
Gallbladder, can it empty through duodenal biliary drainage?, is it the source of B bile?	147	Joannides, M	Relation of hiatus esophageus of diaphragm to stomach, an important function of pillars of diaphragm	61		
experimental bile peritonitis and its treatment in dog	114	Joints, and blood, bacteriology of, in chronic infectious arthritis		571		
Gibb, W F, Jr	Diabetes mellitus study of 147 autopsies	376	Karr, W G	Effect of synthalin on respiratory quotient of the diabetic patient	384	
Glycosuria	See Dextrose, tolerance			Opium addiction, the blood of the human addict during administration of morphine	684	
Goldberg, S E	Ochronosis, report of case of carbolochronosis	196	Kerr, W J	Radicular syndrome in hypertrophic osteo-arthritis of spine, an analysis of 30 cases	212	
Gunther, L	Radiculär syndrome in hypertrophic osteo-arthritis of spine, an analysis of 30 cases	212	Kessler, H H	Some medicolegal aspects of occupational disease	874	
Hamburger, W W	Heart in thyroid disease, changes in T wave of human electrocardiogram following iodine medication and thyroidectomy	35	Koontz, A R	Mustard gas and tuberculosis, an experimental study	90	
Harkavy, J	Pathogenesis of aspiratory abscess of lung, its possible relation to abscess of lung following tonsillectomy	767	Kornblum, K	Chronic pulmonary infection due to the Friedlander bacillus, a clinical and roentgenologic study	351	
Heart	See also Arrhythmia		Kuramochi, K	Pancreatic function, humoroneural regulation of gastric, pancreatic and biliary secretions	446	
block, experimental	184			Pancreatic function, pancreatic secretion in disturbed gastric secretion	413	
cardiovascular problem in pneumonia	249		Lev, M W	Heart in thyroid disease, changes in T wave of human electrocardiogram following iodine medication and thyroidectomy	35	
effect of roentgen rays on, microscopic changes in heart muscle of rats and of rabbits following a series of exposures	15		Levy, R L	Impaired auriculoventricular conduction in rheumatic fever, a comparative study with diagnostic applications	267	
failure, of childhood, clinical types of edema in	795		Light, A B	Opium addiction, circulation and respiration of human addicts during administration of morphine	556	
gallop rhythm in hypertension	166			Opium addiction, conduct of the addict in relation to investigative study	206	
impaired auriculoventricular conduction in rheumatic fever	267			Opium addiction, miscellaneous observations on human addicts during the administration of morphine	878	
in thyroid disease, changes in T wave of human electrocardiogram following iodine medication and thyroidectomy	35			Opium addiction, physical characteristics and physical fitness of addicts during administration of morphine	326	
premature beats clinical significance of, with particular reference to heart rate	606			Opium addiction, the blood of the human addict during the administration of morphine	684	
Horrall, O H	Experimental bile peritonitis and its treatment in the dog	114		Liver, hepatic disorders, including migraine, character of blood lipids in	715	
Houser, K M	Identity of so-called agranulocytic angina, report of case	533		Logan, V W	Diabetes mellitus, study of 147 autopsies	376
Howard, H C	Heart in thyroid disease changes in T wave of human electrocardiogram following iodine medication and thyroidectomy	35		Lundy, C J	Experimental heart block	184
Huntsinger M E	Studies in fat metabolism, the character of blood lipids in hepatic disorders including migraine	715		Lungs, abscess respiratory, pathogenesis of, its possible relation to abscess of lung following tonsillectomy	767	
Hyperbilirubinemia	See Jaundice				bronchogenic squamous cell carcinoma associated with pleural effusion and pulmonary osteo-arthropathy, with features that simulated infection by endameba histolytica	516
Hypertension	See Blood Pressure				chronic pulmonary infection due to Friedlander bacillus, clinical and roentgenologic study	351
Imazu, T	Pancreatic function, pancreatic secretion in disturbed gastric secretion	413				
Insulin, in acromegalic diabetes	785					
Iodine, medication, changes in T wave of human electrocardiogram following thyroidectomy and	35					
Jacobs, M F	Perforations of colon in chronic ulcerative colitis	483				
Jaundice hyperbilirubinemia in peptic ulcer	129					



# INDEX TO VOLUME 43

	PAGE		PAGE
Lyon B B V Can the gallbladder empty through duodenal biliary drainage? is the gallbladder the source of B' bile?, cholecystographic study of biliary drainage	147	Okada, S Pancreatic function, humoro-neural regulation of gastric pancreatic and biliary secretions	446
McClure, C W Studies in fat metabolism character of blood lipids in hepatic disorders including migraine	715	Pancreatic function, pancreatic secretion in disturbed gastric secretion	413
McDowell A M Normal rhythm of white blood cells in women	68	Osinoue T Pancreatic function, humoro-neural regulation of gastric, pancreatic and biliary secretions	446
Martin L Effect of parenteral injections of purified milk proteins on symptoms and progress	299	Opium addiction circulation and respiration of human addicts during administration of morphine	556
Matsubara M Pancreatic function, pancreatic secretion in disturbed gastric secretion	413	addiction, miscellaneous observations on human addicts during the administration of morphine	878
Measles cultural and serologic reactions with green producing micrococci from	274	addiction physical characteristics and physical fitness of addicts during administration of morphine	326
Metabolism in pernicious anemia	488	physical fitness of addicts during administration of morphine	326
Micrococci See Bacteria		addiction conduct of addict in relation to investigative study	206
Migraine character of blood lipids in hepatic disorders including	715	addiction the blood of the human addict during administration of morphine	684
Miller M W Normal blood determinations in the South	96	Oppenheimer E T Gallop rhythm in hypertension	166
Mills R G Bronchogenic squamous cell carcinoma, report of case associated with pleural effusion and pulmonary osteoarthropathy with features that simulated infection by endameba histolytica	516	Osteoarthritis hypertrophic of spine radical syndrome in	212
Mond H Gallop rhythm in hypertension	166	Osteo-Arthritis See Osteoarthritis	
Monroe R T Peptic ulcer a study of 556 cases	846	Otto H L The discordant electrocardiogram	549
Morphine circulation and respiration of human addicts during administration of miscellaneous observations on human addicts during administration of physical characteristics and physical fitness of addicts during administration of the blood of human addict during administration of	556 878 326 684	The ventricular electrocardiogram, an experimental study	335
Mumey N Bronchogenic squamous cell carcinoma, report of case associated with pleural effusion and pulmonary osteoarthropathy with features that simulated infection by endameba histolytica	516	Pachard M Aneurysm of coronary arteries	1
Mustard Gas tuberculosis and	90	Pancreas function pancreatic secretion in disturbed gastric secretion	413
Nachamie I Coarctation of aorta, case of adult type in child 6 months of age	420	humoroneural regulation of gastric pancreatic and biliary secretions	446
Nephritis the Andrewes Diazo reaction in	472	Peptic Ulcer, chloride metabolism and alkalosis in alkali treatment of effect of parenteral injections of purified milk proteins on symptoms and progress	615 299
Nicholls E E Bacteriology of blood and joints in chronic infectious arthritis	571	hyperbilirubinemia in study of 556 cases	129 846
Nelson J M Clinical spirometry, spirometry and their significance	132	Peritonitis bile experimental, and its treatment in dog	114
Noble A Cultural and serologic reactions with green producing micrococci from measles	274	Peters J P Cutaneous and venous blood sugar curves in benign glycosuria and in diabetes	633
Occupational Diseases some medicolegal aspects of	874	Petty O H Effect of synthalin on respiratory quotient of the diabetic patient	384
Ochronosis, report of case of carbolochnosis	196	Phenobarbital, poisoning fatal, report of case with toxicologic analysis	85
		Pleura, bronchogenic squamous cell carcinoma associated with pleural effusion and pulmonary osteoarthropathy with features that simulated infection by endameba histolytica	516
		Pneumonia cardiovascular problem in Friedlander bacillus, chronic pulmonary infection due to	249 351

# INDEX TO VOLUME 43

	PAGE		PAGE
Pohle, E A Effect of roentgen rays on heart, microscopic changes in heart muscle of rats and rabbits following a series of exposures	15	Sturtevant, M Hyperbilirubinemia in peptic ulcer	129
Poisoning See Phenobarbital		Suprarenals the adrenal glands	733
Priest W S Heart in thyroid disease, changes in T wave of human electrocardiogram following iodine medication and thyroidectomy	35	Synthalin, effect of on respiratory quotient of diabetic patient	384
Rablowitch, I M Cholesterol content of blood plasma in diabetes mellitus statistical study based on 2 000 observations in 385 cases	363	Thalheimer, E J Cutaneous and venous blood sugar curves in benign glycosuria and in diabetes	633
Cholesterol content of blood plasma in juvenile plasma, a statistical study	372	Thomas W A Albuminuria in mechanism of detoxification	139
Ramph, B M Cardiovascular problem in pneumonia	249	Thyroid, heart in, changes in T wave of human electrocardiogram following iodine medication and thyroidectomy	35
Respiration, excursion of costal margins in health and in disease	187	Tonsillectomy, pathogenesis of aspiratory abscess of lung, its possible relation to abscess of lung following	767
Respiratory Tract, colds and asthma associated with colds, preventive treatment with vaccines	429	Torrance, E G Opium addiction, circulation and respiration of human addicts during administration of morphine	556
Rheumatic Fever impaired auriculoventricular conduction in, comparative study with diagnostic applications	267	Opium addiction, conduct of addict in relation to investigative study	206
Ri A R Rôle of allergy in tuberculosis	691	Opium addiction, miscellaneous observations on human addicts during the administration of morphine	878
Roentgen Rays effect of on heart, microscopic changes in heart muscle of rats and rabbits following a series of exposures	15	Opium addiction, physical characteristics and physical fitness of addicts during administration of morphine	326
Roche, E Identity of so-called agranulocytic angina, report of case	533	Opium addiction, the blood of the human addict during the administration of morphine	684
Roeburn, M K Cutaneous and venous blood sugar curves in benign glycosuria and in diabetes	633	Tsukahara, T Pancreatic function humoneural regulation of gastric pancreatic and biliary secretion	446
Roth P Clinical spirometry, spiograms and their significance	132	pancreatic function, pancreatic secretion in disturbed gastric secretion	413
Ross, A M Correction of aorta, case of adult type in child 6 months of age	420	Tuberculosis, mustard gas and role of allergy in	90 691
Schmidt, E G The Andrewes Diazo reaction in nephritis	472	Turner, K B Impaired auriculoventricular conduction in rheumatic fever, a comparative study with diagnostic applications	267
Schumann, C Effect of synthalin on respiratory quotient of the diabetic patient	384	Ulrich, H Insulin in acromegalic diabetes	785
Schott, E L Reducing power (blood sugar) of filtrates from blood of rabbit	393	Vaccines preventive treatment for colds and asthma associated with colds	429
Serum, treatment, specific, in chronic ulcerative colitis	50	Walker I C Colds, and asthma associated with colds, preventive treatment with vaccines	429
Smith C Normal rhythm of white blood cells in women	68	Wallace R P Hyperbilirubinemia in peptic ulcer	129
Spine, radicular syndrome in hypertrophic osteo-arthritis of	212	Warthun, A S Effect of roentgen rays on heart, microscopic changes in heart muscle of rats and of rabbits following a series of exposures	15
Spirometry, clinical, spiograms and their significance	132	Wechsler H F Aneurysm of coronary arteries	1
Stainsby, W J Bacteriology of blood and joints in chronic infectious arthritis	571	Welker, W F Albuminuria in mechanism of detoxification	139
Stewart, G N The adrenal glands	733	White P D Auricular fibrillation results of 7 years experience with quinidine sulphate therapy (1921 to 1925)	653
Stomach, humoneural regulation of gastric pancreatic and biliary secretion relation of hiatus esophageus of diaphragm to, important function of pillars of diaphragm	61		
Streptococci, bacteriology of blood and joints in chronic infectious arthritis	571		

# INDEX TO VOLUME 43

	PAGE		PAGE
White P D—Continued		Wolff, L	Auricular fibrillation, results of
Clinical significance of premature beats		7 years experience with quinidine sul-	
with particular reference to heart rate	606	phate therapy (1921 to 1928)	653
Wildman H A		Woodruff, L W	Experimental heart block
Chloride metabolism and		Wright H N	Fatal phenobarbital poison-
alkalosis in alkali treatment of peptic		ing, report of case with toxicologic	
ulcer	615	analysis	85
Wilson J L		Yater W M	Pathologic changes in
Excursion of costal margins		auricular fibrillation and in allied	
in health and in disease	187	arrhythmias	808
Wintrobe M M			
Normal blood determina-			
tions in the South	96		

